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Epidural anaesthesia with levobupivacaine and ropivacaine : effects of age on the pharmacokinetics, neural blockade and haemodynamics

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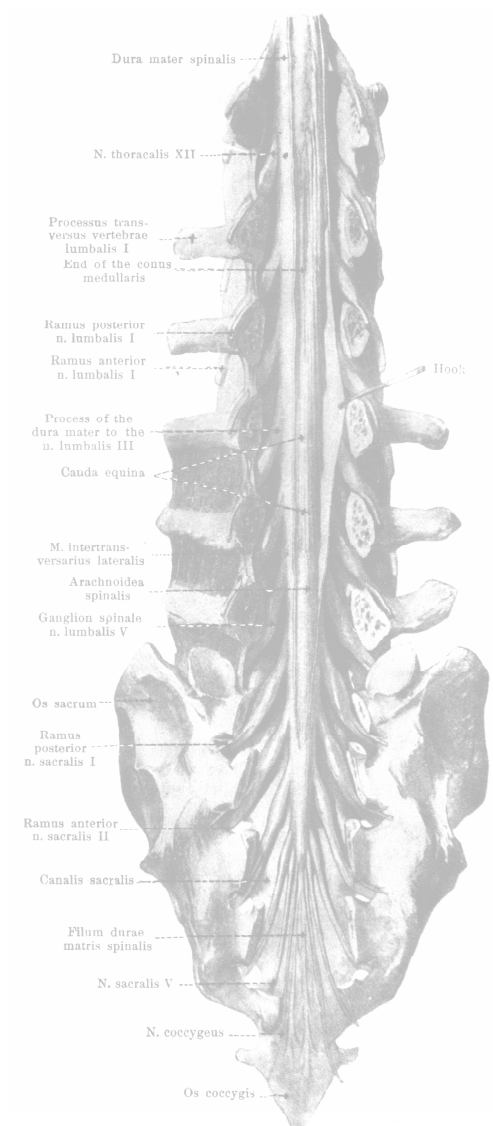
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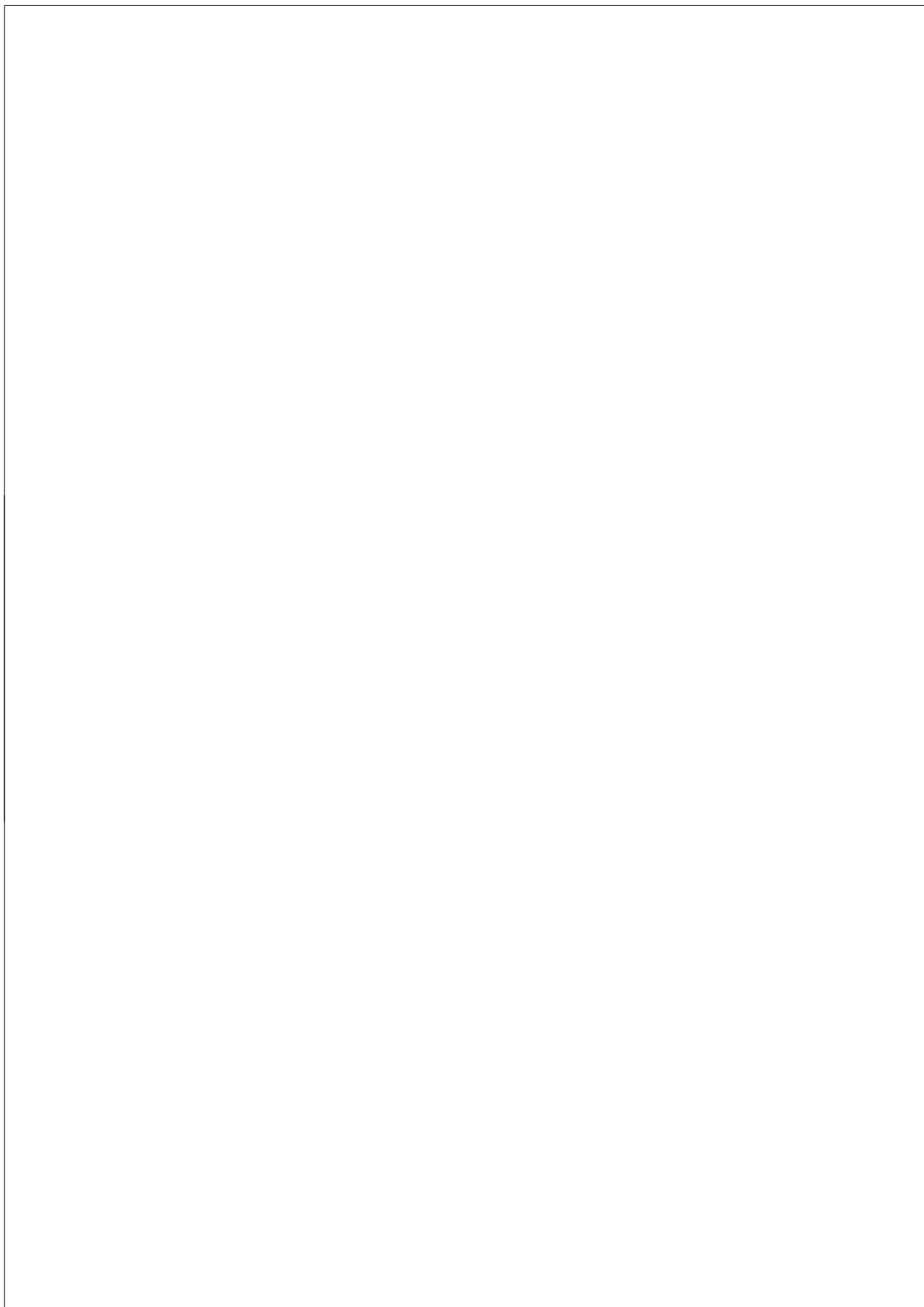
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Section I



Introduction



**ANATOMY AND PHYSIOLOGY OF THE EPIDURAL AND
SUBARACHNOID SPACES**

CHAPTER 1

Anatomy of the epidural space

Knowledge of the anatomic dimensions of the epidural space and its contents is important in understanding the processes which ultimately lead to the nerve blocking actions induced by local anaesthetics. Therefore, in the following section the anatomy of the epidural space will be described, with the emphasis on the lumbar epidural space since this the site of administration in our studies that will follow. The epidural space extends from the foramen magnum to the sacrococcygeal membrane. It is limited at the outside by bony (the laminae, the transverse and spinal processes, the pedicles and the vertebral body) and fibrous (ligamenta flava and posterior longitudinal ligament) structures, which form the vertebral canal (Figure 1).¹ From the inside, the epidural space is limited by the dura mater, which encloses the spinal column and the cerebrospinal fluid (CSF). The vertebral canal changes from oval in the upper lumbar region to a triangular or trefoil shape in the lower lumbar region.^{2,3}

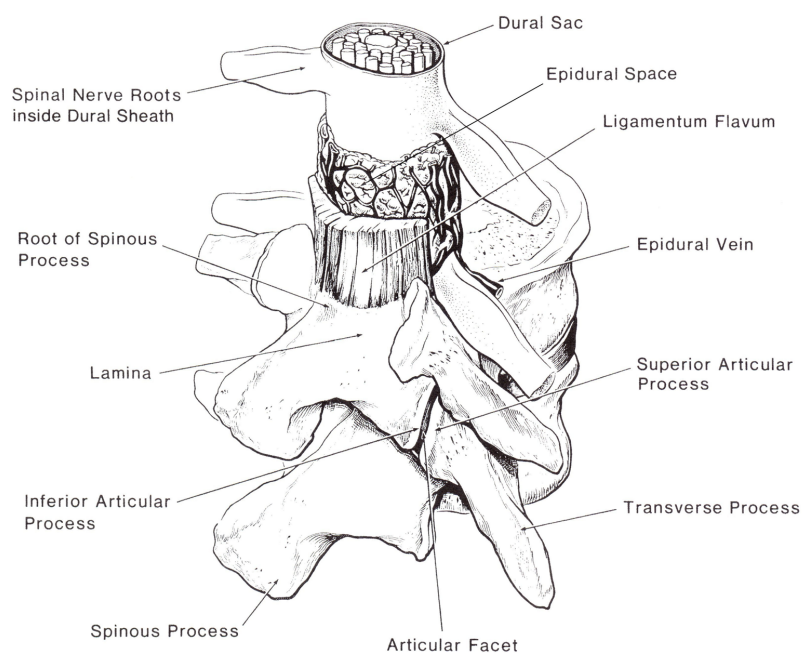


Figure 1. The relationship of the epidural space with the vertebral canal and the subarachnoid space (Cousins MJ, Veering BT. Epidural neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural blockade in clinical anaesthesia and management of pain*. Third edition. Philadelphia, USA: Lippincott-Raven Publishers, 1998; 243-321).¹

The lumbar epidural space has been studied in the past by a variety of techniques, such as anatomical studies on cadavers,² resin casts of the epidural space⁴ and radiographic studies.⁵ More recently, the structural relationships between the contents of the epidural space and the surrounding tissues were investigated by endoscopic examination,⁶⁻⁹ computed tomography (CT)^{3,10} and cryomicrotome dissection.¹¹

Cryomicrotome dissection, in which cadaveric material is frozen *in situ*, revealed a repeated metameric segmentation of the lumbar epidural space in the longitudinal axis (Figure 2).^{11,12} Circumferentially discontinuous compartments, giving rise to an anterior, lateral and posterior compartment, could be identified. These were separated by zones where the dura contacts the canal wall.^{2,3,11,12} A recent anatomic study using CT-imaging confirmed the segmented composition of the epidural space.³

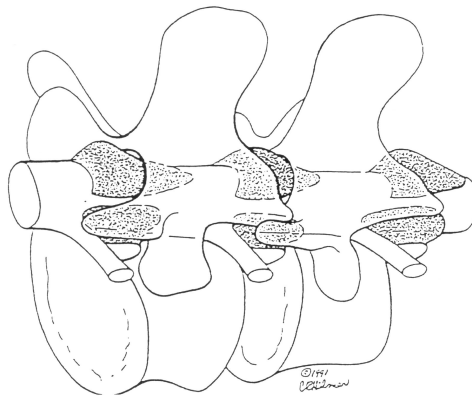


Figure 2. Schematic representation of the compartments of the epidural space, based on observations after cryomicrotome dissection. The epidural contents are discontinuous circumferentially, and repeated metamerically (Hogan Q. *Anesthesiology* 1991; 75: 767-775).¹²

Posterior compartment

On cryomicrotome dissection the posterior compartment of the lumbar epidural space was found between the middle of one lamina and the cephalad edge of the next lower lamina, and limited dorsally by the ligamenta flava.¹² It contains a triangular homogeneous fat pad, without fibrous segmentation and enclosed in a single-layer epithelium.^{2,11,12} The posterior fat pad is attached dorsally through a pedicle-like structure, that is often entered by an artery and vein.¹² Dorsal midline structures, such as connections between the dura

and the posterior boundary of the epidural space or a dorsomedian fold (plica mediana dorsalis), possibly impeding the spread of local anaesthetics, have been observed on epiduroscopy,¹³ CT-epidurography¹⁰ and canalography.⁵ Others observed frail attachments between the dorsal dura and the fat on cryomicrotome dissection.¹⁴ No dorsal midline fold of dura mater was observed in a recent study, using computerized axial tomography without epidurally administered contrast media.³ The presence of vessels in the posterior compartment appears to be irregular,^{2,12,13} but large distended veins,⁶ as well as large veins in the ligamentum flavum^{13,15} have been observed during epiduroscopy.

Lateral compartment

The lateral compartment is formed medial to the intervertebral foramina and is filled with segmental nerves, vessels and fat.^{3,11} This fat is lobulated by septa. From the exiting nerve root to the posterior longitudinal ligament a plane of septation has been observed.

Anterior compartment

The anterior or ventral compartment contains virtually no other structures than vessels, forming a venous plexus originating from the basivertebral vein.¹¹ The posterior longitudinal ligament structure adheres closely to the dura and at the level of a disc it blends into the annular ligament. Caudally from the level of the L4-L5 disc an epidural space filled with fat is present.^{3,12}

Anatomic considerations of the spinal meninges, the cerebrospinal fluid (CSF), and the spinal nerve roots

Before local anaesthetics are able to exert their neuron-blocking activities after epidural administration, they have to cross the spinal meninges. These form a barrier for local anaesthetics to enter their sites of action. Therefore, the anatomy of the spinal meninges and the spinal nerve roots will be described subsequently.

Dura Mater

The dura mater is composed of mainly acellular sheets of collagen, elastin fibres and ground substance, forming concentric lamellae.¹⁶⁻²⁰ The dura mater has an extensive capillary network, which is believed to supply the arachnoid mater.^{17,20} The dura is firmly adhered to the outer layer of the arachnoid mater, leaving no space between the arachnoid

and the fibrous dura.¹⁷ In rats, dural vessels have been found in close relation with unmyelinated nerve fibres, suggesting a role in the nervous control of blood flow and vessel permeability.²¹

Arachnoid Mater

The arachnoid mater can be divided into different layers.^{17,21} The most distinctive layer is the arachnoid barrier cell layer (ABC-layer), which consist of several tiers of tightly packed cells connected not only by desmosomes and gap junctions, but also by tight junctions.¹⁷ A continuous basal lamina divides the ABC-layer from an inner layer, consisting of loosely arranged interweaving trabecular cells which are connected by desmosomes.

Pia Mater

The pia mater, which covers the surface of the spinal cord, is just one cell layer thick and fenestrated.

Arachnoid granulations

Arachnoid granulations are protrusions of the subarachnoid space into the venous sinuses, present between the brain and the skull.²² They consist of penetrations of the arachnoid mater, through the dura, which fuse with the endothelial lining of the venous sinuses. Likewise, arachnoid villi are extensions of the subarachnoid space, penetrating the dura and epidural veins or epidural space at the sites of the root sleeves. They can be regarded as pressure-dependent one-way valves, transferring fluid from the subarachnoid space to the venous system.

Cerebrospinal fluid (CSF)

The cerebrospinal fluid is produced by the choroid plexuses of the four ventricles of the brain and is absorbed by the arachnoid granulations, draining in the venous sinuses present beneath the skull. The CSF is leaving the brain at the bottom of the fourth ventricle through the medial and lateral apertures to embed the spinal cord. Cerebrospinal fluid is displaced downwards into the spinal canal by the pulsatile flow of blood in the central nervous system (CNS) and especially the brain.^{20, 23}

Spinal nerve roots

Spinal nerve roots, leaving the spinal cord consist of fasciculi, which are grouped to 1 or 1-5 bundles (ventral *versus* dorsal root, respectively).¹⁴ These are surrounded by a thin membrane, which are a continuation of the pia-arachnoidea. When the nerve roots distend more laterally, the membranes fuse to surround the fasciculi. When they leave the sac, a deep protrusion of the dura embeds the exiting roots. The inner lamellae of the dura form the walls of the dural sleeves, encasing the spinal nerve roots. They are continuous with the capsules of the dorsal root ganglion and peripheral nerve sheets, forming the epineurium.^{21,24} When the nerve roots spread more laterally, the bundles dissociate into their individual fasciculi. These are separated from each other by connective tissue and surrounded by an extension of the subarachnoid space. These extensions end before the fasciculi reach the dorsal ganglion.¹⁴

Physiologic considerations of the spinal meninges and the cerebrospinal fluid (CSF)

The spinal meninges execute a number of important functions for the central nervous system. They provide mechanical, thermal and immunological protection, nutrition and disposal of waste.²⁵ The close anatomical relationship between the components of the spinal meninges, in particular the dura and arachnoid mater, brings about that they have to be regarded as one physiologic entity. However, they also impede the transport of local anaesthetics to their sites of action. Therefore, recent insights in the physiologic processes that influence the drug transfer will be described.

Diffusion of local anaesthetics and spinal meningeal permeability

Diffusion is defined as the unrestricted migration of molecules or ions through a fluid medium under the influence of the concentration gradient. Permeability is the process of penetration of a barrier, that occurs when the drug passes through a tissue restricting free molecular movement.²⁶ It has been shown that probably not the dura mater, but the arachnoid mater is the major barrier to penetration.^{27,28} The low permeability of the arachnoid mater originates from the presence of partly covering sheets of flattened epithelium-like cells, adhered together with tight and occluding junctions.^{17,20} For that reason, paracellular transport of ions is not likely to occur.²⁸ The pia mater does not oppose diffusion greatly.²⁰ However, studies on the permeability of the spinal meninges have presented conflicting results, which can be attributed to differences in study-design, in particular whether studies were carried out *in vitro* or *in vivo*.

In vitro experiments

In vitro determination of the penetration of the spinal meninges for local anaesthetics was employed using a diffusion chamber apparatus. One study showed that the penetration of the dura by certain opioids and local anaesthetics is independent from the molecular weight or lipid-solubility and can be described as a simple diffusion process.²⁹ In spite of this, another study, using the spinal meninges (dura, arachnoid and pia mater), confirmed the independence of the permeability from molecular size, shape and weight, but showed a relation between hydrophobicity (measured as the octanol:aqueous buffer distribution-coefficient) and the permeability-coefficient.³⁰ This relationship was bi-phasic, meaning that with increasing hydrophobicity the permeability also increases until a maximal meningeal permeability has been reached. Then, with still further increasing hydrophobicity, the meningeal permeability decreases (Figure 3).³⁰ This bi-phasic relationship was confirmed in a recent study.²⁸

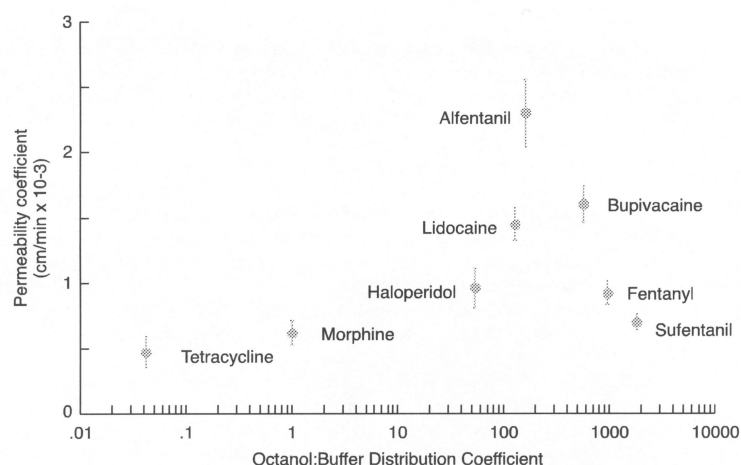


Figure 3. The relationship between hydrophobicity (expressed as the octanol:buffer distribution coefficient) and drug permeability through the intact meninges of the monkey *in vitro* (Bernards CM. *Best Pract Res Clin Anaesthesiol* 2002; 16: 489-505).²⁰

In vivo experiments

In vivo experimental data of the permeability of the spinal meninges for local anaesthetics in human beings are lacking. Using microdialysis in rabbits and investigating the *in vivo* drug transfer rate through spinal meninges of a series of six homologous amide local

anaesthetics, Clement *et al.*²⁸ demonstrated a linear decrease in apparent absorption rate with increasing lipophilicity (Figure 4). This is in contrast with the parabolic relationship observed between the *in vitro* apparent permeability and lipophilicity. This discrepancy can be explained by several competitive processes involved in the epidural disposition, which occur *in vivo*. These factors involved with local tissue distribution are described in more detail in Chapter 2 (Local tissue distribution).

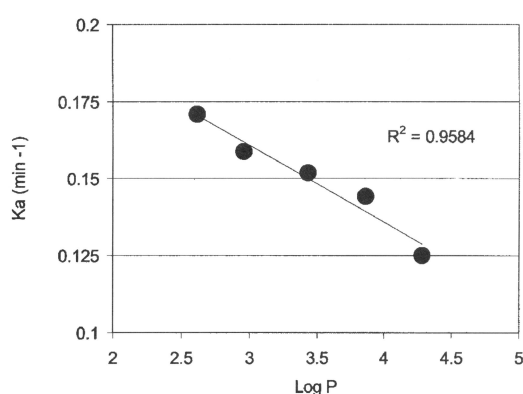
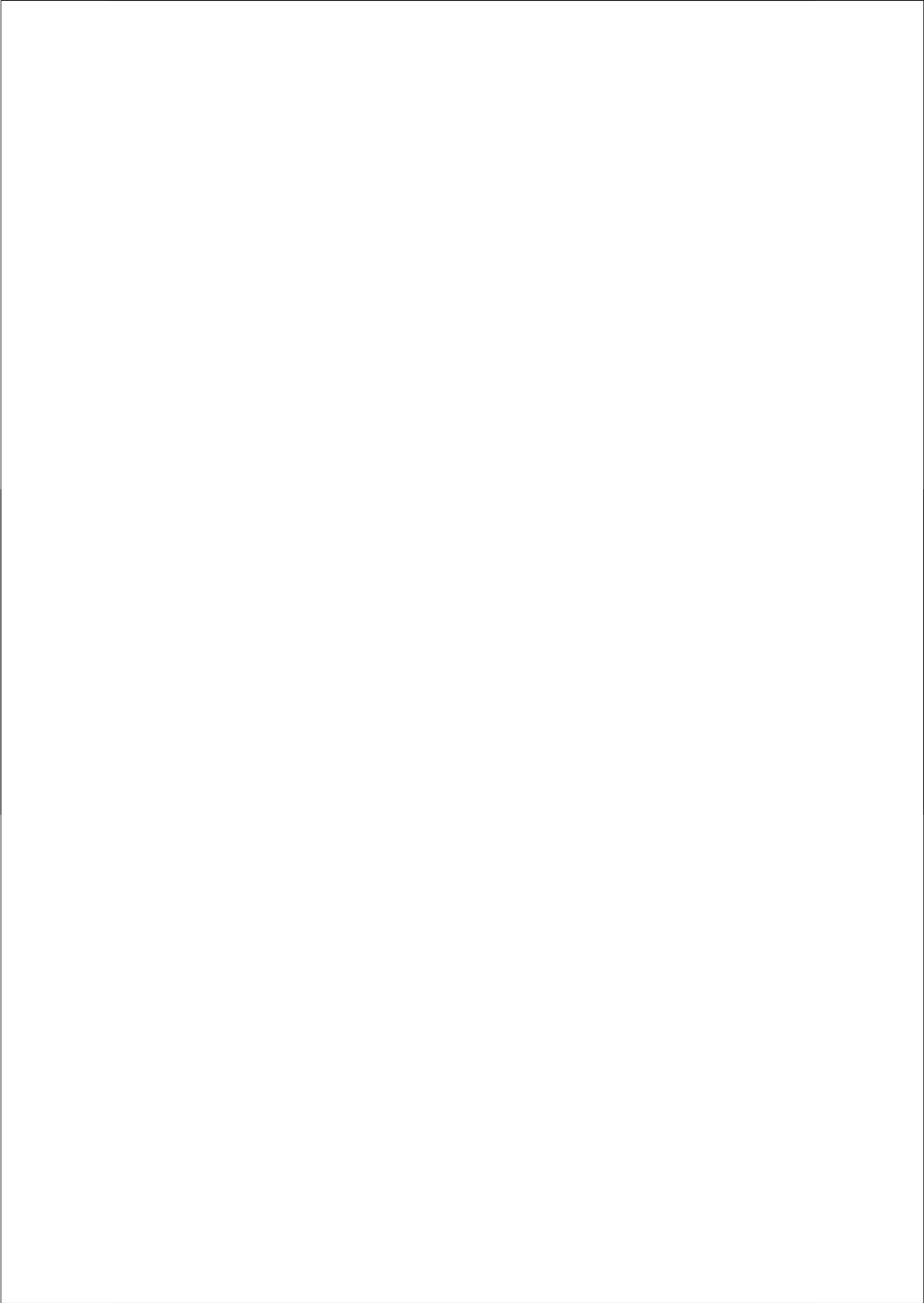


Figure 4. The relationship between the *in vivo* absorption rate constant (K_a) through the spinal meninges in rabbits and log P (the logarithm of the octanol:buffer partition coefficient) of homologous pipecoloxylidide local anaesthetics (Clement R. *Pharm Res* 2004; 21: 706-16).²⁸

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CHAPTER 2

LOCAL ANAESTHETICS AND EPIDURAL ANAESTHESIA: MECHANISMS, SITES OF ACTION AND PHARMACOKINETICS

Epidural anaesthesia is obtained by injection of local anaesthetic drugs into the epidural space within the spinal canal. Some characteristics of local anaesthetics will be described.

Mechanisms of the nerve blocking properties of local anaesthetics

Local anaesthetics act by interaction with the voltage-gated sodium-ion channels (Na^+ -ion channels).¹ They reduce the peak permeability for sodium-ions (P_{Na}) of the axonal membrane, impeding the generation as well as the propagation of action potentials in nerve fibres.²

Historically, two theories have been proposed as possible explanations of the action of local anaesthetics on sodium channels. The first presumes a non-specific mechanism, in which the perturbation of the lipids surrounding the Na^+ -ion channel, leads to the closure and non-functioning of the Na^+ -ion channel.³ The second proposes a direct binding of local anaesthetic molecules to specific receptors on the sodium channel.²

Cationic or protonated forms of the tertiary amide local anaesthetics seem to be the strongest Na^+ -ion channel inhibitors. They act only from the cytoplasmatic side and they reach the binding side by a hydrophilic pathway.¹ However, the uncharged molecule of the local anaesthetic has also (non-specific) nerve-blocking properties. As they are lipid-soluble, their action is probably situated in the cell membrane, whether by gaining access to the binding site by the hydrophobic route or by membrane perturbation.⁴

Clinically useful or tertiary amine local anaesthetics exert their inhibiting actions in two ways: tonic inhibition, occurring after infrequent depolarisation and phasic inhibition, which result from increased frequency of depolarisation.¹ The latter has also been referred to as use-dependent block. Local anaesthetics have different degrees of tonic and phasic block. Local anaesthetics bind selectively to different conformational states (resting, open or inactivated states) of the Na^+ -ion channel, which can be explained by the 'modulated receptor' hypothesis. This means that the binding site changes during the channel's conformational transitions. An alternative theory, the 'guarded receptor' theory, suggests that the affinity for the binding site does not change, but that access of local anaesthetics to the receptor is guarded by the channel's conformation.

Not only the function of Na^+ -ion channels is impeded by local anaesthetics, but also that of other ion-channels (K^+ -, Ca^{2+} -ion channels) and membrane-associated proteins, involved in second-messenger systems or acting as ion-pumping enzymes. This non-specific binding to a variety of structures is likely to occur during spinal and epidural anaesthesia, possibly contributing not only to the nerve blocking effects, but also to the

toxic side-effects on brain and myocardium.¹ Binding affinities of a local anaesthetic are stereoselective.⁵ This will be discussed in Chapter 3.

Sites of action

Local anaesthetics may act on the periphery of the spinal cord, the spinal roots, the dorsal root ganglia and the extradural nerves.⁶ However, the spinal nerve roots, at the location where they leave the subarachnoid space and enter the nerve root sheath, are suggested to be the primary sites of action during spinal and epidural anaesthesia.^{6,7} This is substantiated by significantly higher tissue concentrations in the intradural spinal roots than in the spinal cord^{8,9} and the close proximity of the epidural space and the nerve roots.⁷ Both dura and arachnoidea mater appear to be thinner in this region.^{10,11} In addition, the diffusion surface is increased by the dispersion of the bundles into individual fascicles.⁷ Furthermore, extensions of the subarachnoid space provide a large area for penetration of the local anaesthetic into the nerve structures and also possibly provide retaining pockets of high concentration of local anaesthetics, limiting dilution into a greater pool of CSF.⁷

Despite of lower tissue penetration of local anaesthetics in the spinal cord (with concentration being highest in the lateral and posterior column and lowest in the grey matter),⁸ involvement of the spinal cord in nerve blocking during epidural anaesthesia has been demonstrated.¹²⁻¹⁴ Even lower tissue concentrations have been demonstrated in the dorsal root ganglia after epidural administration of local anaesthetics.⁸ Nevertheless, this site has also been proposed as the primary site of action.¹⁰

Physicochemical properties of local anaesthetics

The physicochemical properties determine the extend of drug distribution to and from the targets in the axonal membrane and account for differences in potency, onset time and duration of anaesthesia among local anaesthetics (Table 1).^{15,16} Local anaesthetics are commonly weak bases with a $pK_a > 7.4$. Because the (neutral) free base is poorly water-soluble, the amide-type local anaesthetics are dissolved as hydrochloride salts in aqueous solutions.

Table 1. Physicochemical properties of local anaesthetics.(Cousins MJ, Bridenbaugh PO, eds. *Neural blockade in clinical anaesthesia and management of pain*. Third edition. Philadelphia, USA: Lippincott-Raven Publishers, 1998; 55-95)

Agent	Chemical configuration			Physicochemical properties					Biologic properties		
	Aromatic lipophilic	Intermediate chain	Amine hydrophylic	Molecular weight (base)	pK	Partition coefficient	Aqueous solubility	Percent protein binding	Equieffective anaesthetic concentration	Approx.	Site of metabolism
										Anaesth. duration (min)	
Esters											
Benzocaine				165	2.5	81	Very low	?	?	?	widely
Butamben				193	2.3	1028	0.1	?	?	?	?
Procaine				236	9.05	1.7	?	6	2	50	Plasma, liver
Chloro-procaine				271	8.97	9.0	?	?	2	45	Plasma, liver
Tetracaine				264	8.46	221	1.4	75.6	0.25	175	Plasma, liver
Amides											
Prilocaine				220	7.9	25	?	55	1	100	Liver, extra-hepatic tissues
Lidocaine				234	7.91	2.4	24	64	1	100	liver
Etidocaine				276	7.7	800	?	94	0.25	200	liver
Mepivacaine				246	7.76	21	15	77	1	100	liver
Ropivacaine				262	8.2	115	?	95	0.5	150	liver
Bupivacaine				288	8.16	346 1565 ^a	0.83	96	0.25	175	liver
Levo-bupivacaine				288	8.09	1624 ^a	?	>97%			liver

^a Oleyl alcohol partition coefficient

Molecular weight

Molecular weight is not an important factor in determining the differences in permeability among local anaesthetics.^{16,17}

Ionisation and pH

Changes in plasma pH changes the degree of ionisation, which in turn influences lipid-solubility and the activity of local anaesthetics. Moreover, it plays an important role in the determination of the equilibrium between the ionised and non-ionised form in different body compartments. The degree of ionisation of local anaesthetics is quite sensitive to small changes in plasma pH.^{18,19}

Lipid solubility

An increased lipid solubility, measured as the n-heptane/buffer partition coefficient, is *in vitro* associated with an increased partitioning in rat sciatic nerve, human extradural fat and subcutaneous fat.²⁰ Potency has been shown *in vitro* as well as *in vivo* to be related to lipid solubility.^{15,21,22} However, this relationship may be complex, because high lipid solubility enhances the diffusion of the drug into membranes, but may become rate-limited when a large fraction of the local anaesthetic is in the ionised state. Moreover, the faster diffusion rate of the lipid-soluble drug can be counteracted by the capacity of the membrane to contain the drug in its lipophilic environment.¹⁶ Next to a greater lipid-solubility, the longer-acting local anaesthetic show extensive protein binding. Both factors can contribute to a slower net penetration rate.¹⁶

Protein binding

An increase in the degree of protein binding is thought to increase the duration of local anaesthetic activity. Therefore, agents that penetrate the axolemma and attach more firmly to membrane proteins have a prolonged duration of anaesthetic activity.²³

Local drug distribution

Local disposition refers to the processes, which take place after administration of the drug at the site of injection until it reaches the site of action (Figure 1).²⁴

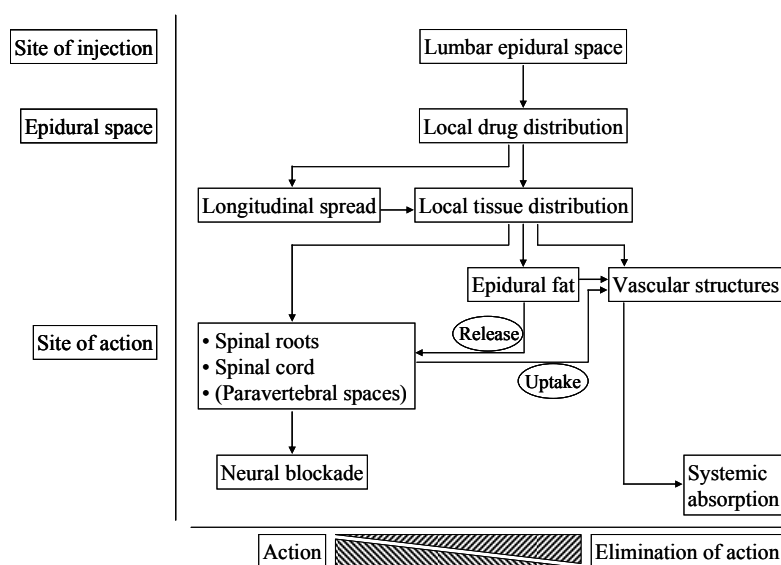


Figure 1. Processes involved in the local disposition after epidural administration of local anaesthetics.

Longitudinal spread

The longitudinal spread of local anaesthetics in the epidural and subarachnoid spaces accounts primarily for the extend of the subarachnoid and epidural neural blockade, although they do not necessarily correspond exactly. This is because diffusion and vascular transport possibly influence the ultimate spread of analgesia.¹⁶ Longitudinal spread has shown to be more in a cephalad than caudad direction^{25,26} and it depends largely on bulk flow during and after administration and on the structures in the epidural space, which resist inflow.^{16,19} In this context, the epidural space can be regarded as a reservoir, which is collapsible, distensible and leaky.²⁷ The spread of analgesia may be modified by outflow of local anaesthetics through the intervertebral foramina. Changes in the anatomy of the intervertebral foramina by disease or advancing age may alter the spread of analgesia by this mechanism.²⁷⁻²⁹

Local tissue distribution

Local anaesthetics reach the spinal roots and the spinal cord from the CSF by passive diffusion.³⁰ Deeper areas of the spinal cord are possibly reached via the spaces of Virchow-Robin, which are extensions of the subarachnoid space, accompanying blood vessels penetrating the spinal cord from the pia mater.³¹ Uptake into spinal radicular arteries may contribute to the deliverance to deeper structures of the spinal cord.^{32,33} On the other hand, it is more likely that local blood flow of the spinal cord plays a role in the vascular removal rather than vascular deliverance of local anaesthetics.^{31,34} Arachnoid villi have also been regarded as potential regions for drug transfer from the epidural space to the CSF and finally to the spinal cord.¹⁰ However, Bernards *et al.*,³⁵ using an *in vitro* model, provided ample evidence that the spinal nerve root sleeve, containing arachnoid villi, did not contribute to the diffusion of certain opioids and lidocaine across the meninges. Another suggested pathway is the leakage of local anaesthetics into the paravertebral space, allowing them to diffuse through the nerve coverings and spread centripetally via the subperineural and subpial spaces.⁶ However, this route seems not to be very important except in young patients.

The nerve blocking effects of local anaesthetics are counteracted by the uptake of the local anaesthetics in epidural fat and vascular structures.³⁶ Uptake in the epidural fat lowers the perineural concentration and thus reduces the clinical potency of a local anaesthetic. Additionally, it may prolong the duration of block, by providing a depot from which the local anaesthetic dissociates slowly, maintaining a clinically significant perineural concentration.¹⁶ The area of the intervertebral foramina, as well as the connective tissue surrounding dural sleeves is found to be highly vascularized,¹¹ favouring the systemic uptake of local anaesthetic.

In vivo data on the local distribution in the epidural space of local anaesthetics are hardly available and *in vitro* (or *ex vivo*) studies may not take into account processes, which may alter the transfer from the site of injection to the site of action. However, two studies, using microdialysis of samples of the epidural and subarachnoid space in rabbits have given insight in the processes, occurring likely *in vivo*.^{30,36} These are (Figure 2).³²

1. Uptake into the CSF after diffusion through the meninges,
2. Uptake into the systemic circulation after diffusion through capillary vessel walls,
3. Distribution into epidural fat.

Following epidural administration, the elimination clearance was higher than the intercompartmental clearance distribution from the epidural to the subarachnoid space for the least lipophilic local anaesthetic whereas the reverse was true for the most lipophilic

one.³⁰ These differences in epidural disposition are probably best explained by the influences of lipophilicity and the consequent differences between local anaesthetics in partitioning into the epidural fat.²⁰ Epidural and intrathecal disposition were sensitive in a similar manner to drug lipophilicity. Also, after both epidural and intrathecal administration of local anaesthetics plasma-concentration curves showed a bi-phasic decline.³⁰ Intrathecal elimination clearance of local anaesthetics was 1.5 to 3 times lower compared to the epidural elimination clearance, which is contributed to the smaller subarachnoid blood flow compared to the epidural blood flow. Bioavailability in the CSF of epidurally administered local anaesthetics is low (<20%). Therefore, elimination from the epidural space is predominantly by uptake in the epidural blood flow.

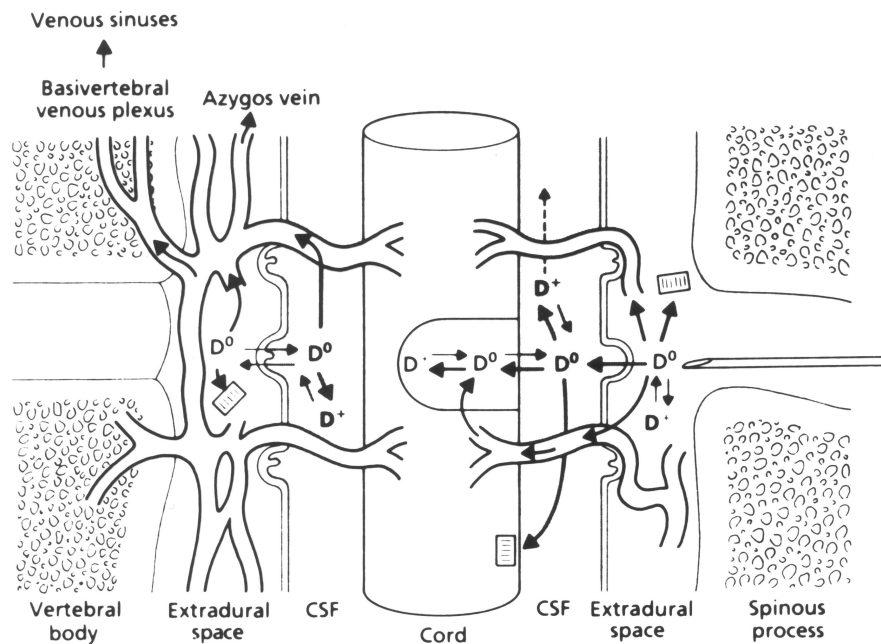


Figure 2. Model of local distribution to the epidural and subarachnoid space and systemic uptake of local anaesthetics after epidural administration (Cousins MJ, Mather LE. *Anesthesiology* 1984; 61: 276-310).³²

The systemic pharmacokinetics of epidurally administered local anaesthetics

Absorption

After epidural and subarachnoid administration, at least 95% of local anaesthetics will be absorbed into the systemic circulation.¹⁹ It is reached by uptake in the epidural veins and subarachnoid blood vessels, in particular those present in the pia mater and the spinal cord. From there the systemic circulation is reached by the azygos vein, which empties into the vena cava superior.^{6,16} Because local anaesthetics are relatively lipid-soluble, the diffusion through the endothelium seems not to be rate-limiting and the absorption rate is mostly dependent on the local blood flow.³⁷

Local blood flow

The perfusion of the epidural vessels may be influenced by the vasoactive properties of local anaesthetics or by the sympathetic block that results from neuraxial blockade. By this mechanism local anaesthetics may influence their own systemic absorption.³⁸ Other factors that may contribute to an altered local perfusion of the epidural space are hypovolemia, effects of added vasoconstrictors, systematically administered drugs and cardiovascular changes due to pregnancy or diseases.

Central neuraxis blockade

Concentration-time profiles after epidural or subarachnoid administration of a local anaesthetic are the net result of uptake (absorption) and distribution and elimination (disposition). Absorption rates cannot be derived directly from the concentration-time profiles, because local anaesthetics exhibit flip-flop kinetics, *i.e.* the absorption phase extends into the elimination phase and therefore rate-limits the elimination.

Previously, the absorption of local anaesthetics has been assessed by measuring peak plasma concentration and time to peak concentrations.³⁸ Although these measurements provided data about the relation between dose, concentration and potential for toxicity, they do not provide information about the absorption processes itself.³⁹ With a deconvolution method of plasma drug concentration-time curves using disposition functions obtained from intravenous data, the systemic absorption of local anaesthetics after intravenous regional anaesthesia and epidural administration could be derived.^{18,40} It occurred that the systemic uptake of lidocaine and etidocaine was a bi-phasic process.

A stable-isotope method, using deuterium-labelled analogues of local anaesthetics, has been developed to study simultaneously the systemic absorption and disposition of these

agents.⁴¹⁻⁴³ In this approach, a stable isotope-labelled analogue of the drug to be studied is administered intravenously at approximately the same time as the unlabelled drug is administered by the extravascular route. The use of this method requires that the unlabelled drug and the stable isotope-labelled analogue have similar distribution and elimination characteristics, *i.e.*, it presumes that labelling of the drug does not influence its pharmacokinetic profile.⁴¹

Using the stable-isotope method, the abovementioned bi-phasic absorption profile has been confirmed by studies investigating the absorption kinetics after epidural (lidocaine,⁴² bupivacaine^{42,44} and ropivacaine,⁴⁵ respectively) and subarachnoid administration (lidocaine⁴³ and bupivacaine,^{43,46} respectively). In these studies a rapid initial phase was followed by a slower second phase for all modes of administration. The fast absorption during the initial phase is probably caused by the high initial concentration gradient.³⁹ Moreover, absorption during the initial phase was much slower after subarachnoid than after epidural administration and even absent for lidocaine. This may be contributed to the difference in vascularity between the epidural and subarachnoid space, the latter being less extensively vascularized.^{19,30} The absence of a difference between the absorption rate during the slow late absorption phase after epidural and subarachnoid administration may reflect the uptake into and slow release from the epidural fat after both routes of administration.³⁷ The difference between lidocaine and bupivacaine, regarding the absorption rate during the slow late absorption phase can be explained by a difference in tissue/blood partition.³⁹

Disposition and protein binding

After systemic absorption local anaesthetics are rapidly distributed to the highly perfused organs (lung, kidney, etc.) and more slowly to less perfused tissues such as skeletal muscle and fat.²³ The amide-type local anaesthetics are relatively lipophilic compounds. Therefore, their tissue distribution is highly dependent upon tissue perfusion.

Amide-type local anaesthetics, being weak basic drugs, bind primarily to the high-affinity, low-capacity binding sites on α_1 -acid glycoprotein.^{19,37,47} In addition, they bind to a lesser extent to the low-affinity high-capacity sites on albumin.¹⁹ Binding of bupivacaine to α_1 -acid glycoprotein approaches saturation at concentrations in the order of $75 \mu\text{g}.\text{ml}^{-1}$. α_1 -acid glycoprotein concentration depends on various factors. Chronic pain and inflammatory diseases, infections, trauma and surgery raise the concentration of α_1 -acid glycoprotein, whereas oral contraceptives, pregnancy and young age are associated with a low concentration.⁴⁷⁻⁴⁹ Protein binding of local anaesthetics has also been shown to be stereoselective.^{50,51} This will be discussed in Chapter 3.

Total plasma concentrations of the local anaesthetics bupivacaine and ropivacaine have been shown to increase in the postoperative period following epidural infusion.^{52,53} After reaching a plateau after the first 12-24 hours, free plasma concentrations of local anaesthetics did not increase. Any further increases in total plasma concentrations are due to the increased protein binding. Changes in protein binding of the local anaesthetics are unlikely to change the plasma concentrations of free bupivacaine and ropivacaine or steady-state distribution of the unbound fraction, because changes in the concentration of free drug are buffered by the high volume of distribution.³⁷

Elimination

Ester-type local anaesthetics are hydrolysed to aminobenzoic acid derivatives by cholinesterases, which are present in plasma, erythrocytes and in the liver. The metabolism is very rapid, being almost completed *in vitro* within 1 minute for procaine and chlorprocaine.³⁸

Biotransformation and clearance of amide-type local anaesthetics can be attributed almost entirely to the liver.³⁹ Renal excretion of unchanged drug accounts only for less than 1-5% of the total clearance.³⁸ There is no or negligible metabolism of amide-type local anaesthetics in the epidural and subarachnoid space, nor evidence for an extrahepatic site of metabolism, except for prilocaine and lidocaine. Common metabolic pathways of amide-type local anaesthetics are aromatic hydroxylation, N-dealkylation and amide hydrolysis. Metabolites present in significant plasma concentrations after continuous infusion may possibly add to the systemic effects of local anaesthetics.¹⁶

The hepatic clearance of amide-type local anaesthetics is influenced by liver blood flow, the intrinsic enzymatic activity of liver tissue and protein binding. Elimination of local anaesthetics with a high extraction ratio (> 70%), such as etidocaine, lidocaine and mepivacaine, depends largely on the liver blood flow, as where those with a low extraction ratio (< 30%), such as bupivacaine depend on protein binding and enzyme activity. Clearance of unbound drug is flow- and binding dependent for high-extraction and dependent on enzyme activity for low-extraction local anaesthetics.³⁷

Factors influencing distribution and elimination

The distribution and elimination of local anaesthetics can possibly be altered by patient-related variables, different states of disease and drug-drug interactions. Diseases, especially severe cardiovascular and liver disease may significantly affect the systemic disposition of local anaesthetics after neuraxial blockade.¹⁶ The direction of changes are

sometimes difficult to predict, because changes in disposition can be counteracted by changes in absorption, in particular when cardiovascular differences occur.³⁹ Furthermore, drugs can interact with the disposition of local anaesthetics by acting on the cardiovascular system, for instance by inhibiting the compensatory mechanisms after neuraxial blockade (pre-medication, β -blockers) or by a direct sympathicomimetic effect. Other mechanisms include induction of enzymes (anticonvulsant medication) or enantiomer-enantiomer interactions (local anaesthetics).¹⁶ Distribution, as well as elimination, show stereoselectivity (see Chapter 3).

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CHAPTER 3

CHIRALITY AND LOCAL ANAESTHETICS

Stereoisomerism: definitions & nomenclatureDefinitions

Stereoisomers have identical sets of atoms configured into the same groups but with a different spatial arrangement.¹ Chirality (derived from the Greek 'cheir' meaning hand), enantiomerism or optical isomerism is a subset of stereoisomerism in which the set of molecules bear a mirror-image relationship to each other (Figure 1). Because they lack a plane of symmetry, enantiomers are not superimposable. This arises from a spatial orientation of four different groups of atoms, attached to an asymmetric centre, usually a carbon-atom.²

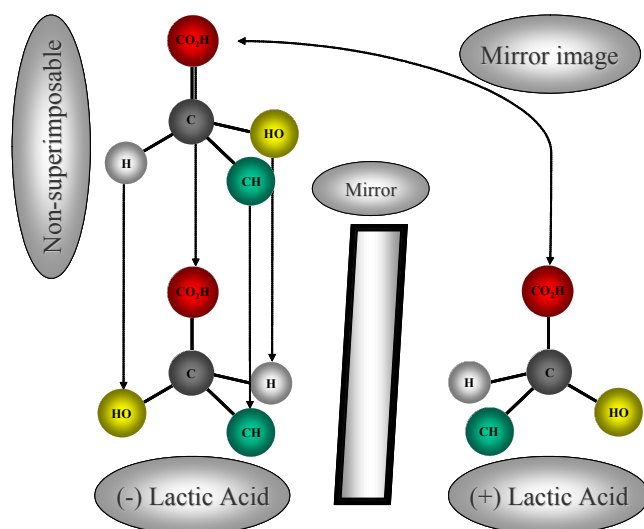


Figure 1. Enantiomers have a mirror-image relationship to each other, and they are not super-imposable.

The physicochemical properties are equal for both enantiomers, but they differ in the way that they rotate plane-polarized light, *i.e.* to an equally extent, but in the opposite direction. Many drugs contain a 50:50% ratio of the enantiomers, which is known as a racemic mixture or racemate.³

Nomenclature

The 'sequence rules' of Cahn, Ingold and Prelog designate the molecular configuration by giving a sequence of priority to the four atoms or groups attached to the tetrahedral asymmetric centre.⁴ The enantiomers are named R- (or Rectus) and S- (or Sinister).¹ In addition, a system of nomenclature based upon the relative direction of rotation (clockwise: +; counterclockwise: -) of plane polarized light is used in conjunction with the abovementioned system. A racemic mixture will be indicated with the prefix 'rac-' or 'RS-'.

Implications of chirality on pharmacokinetic and -dynamic characteristics of drugs

Although enantiomers have the same physicochemical properties, their biological behaviour, in terms of pharmacokinetic and pharmacodynamic characteristics can be very different (Figure 2).⁵⁻⁷ This is caused by differences between the R- and S-enantiomer at the three-dimensional interaction with the asymmetrical receptor, which consists to a large extent of chiral proteins with enantioselective properties.⁷

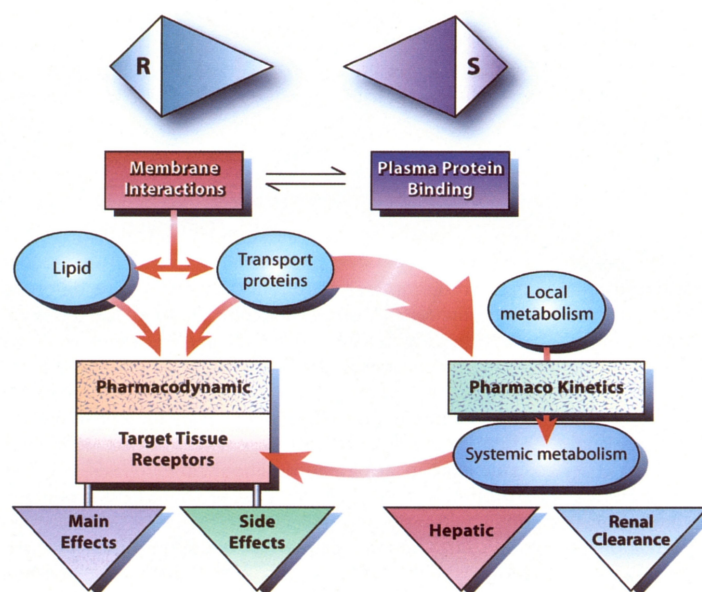


Figure 2. Potential sources of chiral contributions to anesthetic drug actions in vivo (Nau *et al.* *Anesthesiology* 2002; 97: 497-502).⁷

Chirality and local anaesthetics

This section will outline the influence of chirality on the pharmacokinetics and the nerve blocking characteristics of local anaesthetics, in particular of bupivacaine. Subsequently, in the next section the recently introduced local anaesthetics ropivacaine and levobupivacaine will be discussed.

All amide-type local anaesthetics, except for lidocaine, contain a chiral centre. Prilocaine, mepivacaine and bupivacaine are used clinically as racemic mixtures. Although racemic bupivacaine has been used widely for central neuraxis blockade, as well as peripheral nerve blockade, concerns were raised about its cardiotoxicity, in particular after the editorial of Albright.⁸ Racemic bupivacaine was associated with sudden onset of cardiac arrest with minimal or without prodromal central nervous system signs of toxicity, prolonged resuscitation and a high number of maternal deaths after inadvertent intravascular injection.^{8,9} These events stimulated the search for safer local anaesthetics and resulted in the development of local anaesthetic containing only the pure S(–)-enantiomer. Although already developed in 1957, ropivacaine became in 1996 the first clinically available enantiopure local anaesthetic.^{10,11} Recently, the single S(–)-enantiomer of bupivacaine has been put on the market as levobupivacaine.¹²

Influence of chirality on pharmacokinetics

Absorption

Absorption over membrane matrices is in general not enantioselective, because this occurs for most of the drugs by passive diffusion.¹³ Nevertheless, it may be influenced by enantioselectivity, when movement over the membrane is facilitated by active transport. Additionally, absorption can be altered by differences in intrinsic vasoactivity (vasodilatation or vasoconstriction) between enantiomers, possibly influencing local blood flow.

With regard to local anaesthetics, the systemic absorption of local anaesthetics after epidural administration does not seem to be enantioselective. This has been demonstrated for the enantiomers of bupivacaine (R(+)- and S(–)-bupivacaine, respectively) after epidural administration of the racemate (Figure 3).¹⁴ Total peak plasma concentrations of S(–)-bupivacaine were higher than those of R(+)-bupivacaine, which is consistent with the results of Sharrock *et al.*¹⁵ Unbound concentrations of S(–)-bupivacaine were lower than those of R(+)-bupivacaine. Mean absorption time (MAT) was not different between both enantiomers. The observed differences in concentration-time profiles of the enantiomers of bupivacaine were most likely the results of enantioselective disposition.

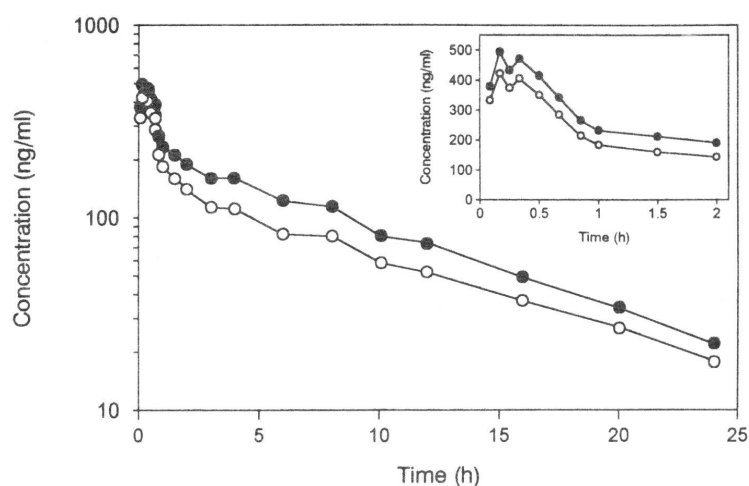


Figure 3. Total plasma concentrations of R(+)-bupivacaine (○) and S(-)-bupivacaine (●) from representative patients after epidural administration of the racemate (Groen *et al. Anesth Analg* 1998; 86:361-6).¹⁴

Disposition

Distribution, as well as metabolism and excretion are enantioselective processes. Binding to plasma proteins has been shown to be enantioselective for a number of drug enantiomers.^{13,16}

With regard to local anaesthetics, human studies show enantioselective disposition.¹⁷⁻¹⁹ Burm *et al.*¹⁷ determined the pharmacokinetics of the enantiomers of bupivacaine after intravenous administration of the racemate. Total plasma concentrations were higher for S(-)-bupivacaine than for R(+)-bupivacaine (Figure 4). On the other hand, the unbound concentration and unbound free fraction of R(+)-bupivacaine were higher than that of S(-)-bupivacaine. Clearance (Cl) and distribution volume at steady state (V_{ss}), based on total plasma concentrations, as well as elimination half-life ($t_{1/2,el}$) and mean residence time (MRT) were significantly greater for R(+)-bupivacaine than for S(-)-bupivacaine. In contrast, the plasma clearance (Cl_u) of unbound R(+)-bupivacaine was significantly lower than that of S(-)-bupivacaine. In addition, the unbound volume of distribution at steady state ($V_{u,ss}$) was not different between both enantiomers. The observed enantioselective effects may be largely attributed to a difference in the degree of plasma binding.¹⁸

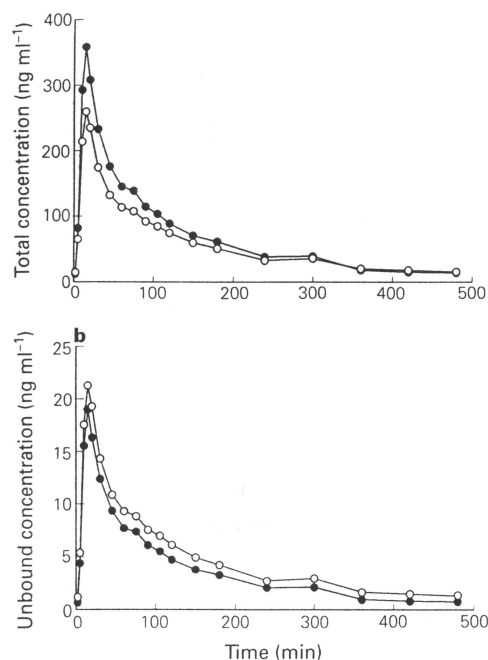


Figure 4. Total (upper panel) and unbound (lower panel) plasma concentrations of R(+)-bupivacaine (○) and S(-)-bupivacaine (●) from representative volunteers after intravenous administration of the racemate (Burm *et al. Br J Clin Pharmacol* 1994; 84: 85-9).¹⁷

Long-term epidural infusion of racemic bupivacaine up to 48 hrs showed a progressive increase in total plasma concentrations of both enantiomers (Figure 5).²⁰ However, the unbound concentrations of the enantiomers remained at a fairly stable level with time. The total plasma concentration of the S(-)-isomer prevailed, compared to that of the R(+)-isomer, as did the unbound concentration of the R(+)-enantiomer, compared to that of the S(-)-enantiomer. The ratio between the total, as well as the unbound concentrations of the R(+)- and S(-)-enantiomer of bupivacaine did not change significantly with time. Also, the ratio of the free fraction of the R(+)- and S(-)-enantiomer did not change with time. At the end of the infusion the Cl_u of S(-)-bupivacaine was higher than that of R(+)-bupivacaine.

Influence of chirality on nerve blockade

Clinical actions of drugs may be strongly influenced by pharmacokinetic processes that themselves are often enantioselective.⁷ This has to be taken into account when assessing possible different clinical effects of enantiomers.

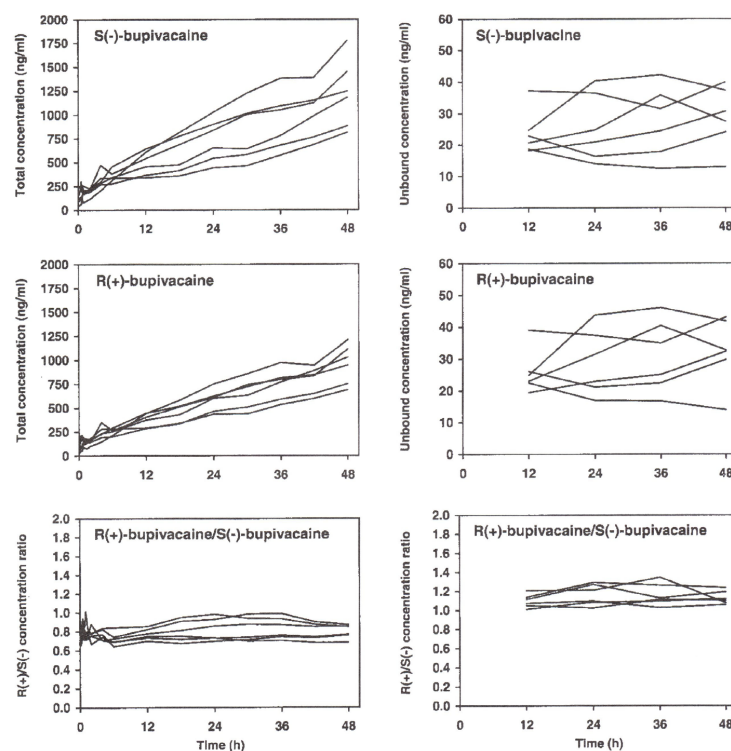


Figure 5. Individual total (left) and unbound (right) plasma concentrations of S(-)-bupivacaine and R(+)-bupivacaine and R(+)-bupivacaine/S(-)-bupivacaine concentration ratios *versus* time (Veering *et al. Anesthesiology* 2002; 96: 1062-9).²⁰

In contrast to early *in vitro* experiments,^{21,22} recent studies on crayfish giant axons or on neuronal sodium channels, using the patch-clamp technique showed some, although weak enantioselective activity. The R-enantiomer of bupivacaine is more potent than the S-enantiomer for tonic block (ratio 1.3-1.6)²³⁻²⁵ and increasingly more potent for phasic block of nerve impulses.^{23,24,26} The latter can be explained kinetically by the slower dissociation of R(+)-bupivacaine from the inactivated channel than S(-)-bupivacaine.

An *in vivo* study, performed in rats showed no differences for R(+)-, S(-)- and RS-bupivacaine in duration of anaesthesia after sciatic nerve block.²² However, after infiltration anaesthesia or intradermal injection, S(-)-bupivacaine showed longer duration of anaesthesia than its antipode.^{22,27} Discrepancy between the results obtained *in vitro* and *in vivo* may be explained by differences between the enantiomers in binding properties and/or in vasoactive properties.²¹

In humans, the potency of S(–)-bupivacaine was greater and the duration of anaesthesia was longer after intradermal injection than for R(+)-bupivacaine.²⁸ This may be explained by differences in vasoactive properties between the two enantiomers.

Influence of chirality on vasoactive properties

The vasoactive properties of local anaesthetics may be important by influencing, to a certain extent, the uptake of the drug into the systemic circulation. This, in turn, influences duration of neural blockade and the risk of systemic toxicity. However, the determination of the vasoactive effect of local anaesthetics is depending on chirality and concentration of the local anaesthetic.²⁹

In general, S(–)-bupivacaine seems to have vasoconstrictive properties, compared to R(+)-bupivacaine.^{27,28,30} In a dog animal model, racemic and R(+)-bupivacaine dilated cerebral pial arterioles, as where S(–)-bupivacaine induced vasoconstriction.³⁰ After intradermal injection in humans, both the enantiomers of bupivacaine showed vasodilatation in high concentrations, whereas S(–)-bupivacaine showed vasoconstriction in the intermediate concentration range.²⁸ Another study showed that the vasoactive effects of both racemic bupivacaine and levobupivacaine are bi-phasic, *i.e.*, they are a vasoconstrictor at low (sub-clinical) concentrations and a vasodilator at high concentrations.²⁹ The longer duration of analgesia after cutaneous infiltration of S(–)-bupivacaine may be caused by its greater vasoconstrictive action, compared to R(+)-bupivacaine.^{27,28}

Unlike bupivacaine, both racemic ropivacaine and the enantiomers of ropivacaine induced vasoconstriction of pial vessels in a dog animal model.^{30,31} The degree of vasoconstriction decreased in the following order: S(–)-ropivacaine > racemic ropivacaine > R(+)-ropivacaine.

Recently introduced local anaesthetics

Ropivacaine

Ropivacaine (S(–)-1-propyl-2',6'-pipecoloxylidide hydrochloride) contains a propyl-side chain, while mepivacaine contains a methyl- and bupivacaine a butyl-side chain to the amino nitrogen of the piperidine ring (Figure 6).^{32,33} The physicochemical properties are similar to those of bupivacaine and levobupivacaine, except for its lower lipid-solubility (Table 1). This may contribute to a greater differential block of sensory and motor function than bupivacaine.¹² However, as lipid solubility is related to potency, ropivacaine may also be less potent.³³

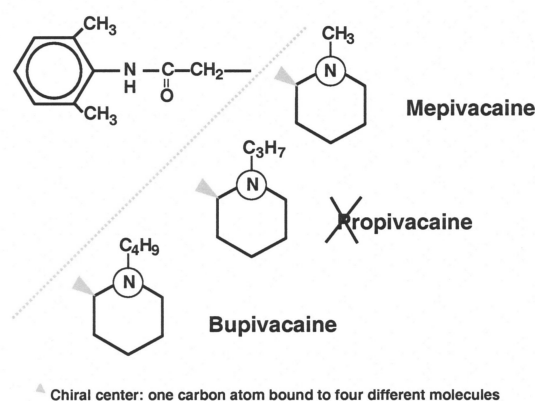


Figure 6. Structure of the n-alkyl-substituted pipercolyl xylidines mepivacaine, ropivacaine and bupivacaine (Casati A, Putzu M. *Best Pract Res Clin Anaesthesiol* 2005; 19: 247-68).³³

Table 1. Physicochemical properties of bupivacaine, levobupivacaine and ropivacaine (Casati A, Putzu M. *Best Pract Res Clin Anaesthesiol* 2005; 19: 247-68).³³

	Bupivacaine	Levobupivacaine	Ropivacaine
Molecular weight	288	288	274
pK _a	8.1	8.1	8.1
Liposolubility	30	30	2.8
Partition coefficient	28	28	9

Pharmacokinetics after intravenous and epidural administration

Pharmacokinetic data of ropivacaine, determined after intravenous infusion.^{34,35} or epidural administration^{36,37} are summarized in table 2 and 3, respectively, and compared with the pharmacokinetics of bupivacaine³⁸⁻⁴⁰ and levobupivacaine.^{41,42} Absorption has shown, like that of bupivacaine, to be bi-phasic. Absorption parameters after epidural administration have been described in young volunteers (Table 3).³⁶ Elimination of ropivacaine is absorption-dependent, which is substantiated by the difference of the terminal half-life ($t_{1/2,el}$) after epidural (5-7h) and intravenous administration (<2 h). Ropivacaine is highly protein bound (approximately 94%).³⁴ Continuous epidural infusion for postoperative pain shows an increasing total concentration of ropivacaine, due to an increase in α_1 -acid glycoprotein.³⁷ However, unbound drug concentration of ropivacaine remained relatively constant.

Table 2. Pharmacokinetic data of bupivacaine, levobupivacaine and ropivacaine, derived after intravenous infusion.

Total plasma concentration	$t_{1/2,el}$ (min)	Cl (ml/min)	V_{ss} (l)	Protein binding (%)
Bupivacaine ^a	162	580	73	95
Levobupivacaine ^b	77	650	67	97
Ropivacaine ^c	98	395	39	94 ^d
Unbound concentration		Cl _u (l/min)	Vu _{ss} (l)	F _u (%)
Bupivacaine ^a			1028	
Ropivacaine ^c		7.9	819	5.1

^a Derived from reference 38 (arterial blood concentration); ^b Derived from reference 41; ^c Derived from reference 35; ^d derived from reference 34; ^{b+c} venous blood concentration.

Table 3. Pharmacokinetic data of bupivacaine, levobupivacaine and ropivacaine, derived after epidural administration.

Total plasma concentration	C _{max} /100 mg drug (µg/ml)	Absorption kinetics			
		F ₁	$t_{1/2,a1}$	F ₂	$t_{1/2,a2}$
Bupivacaine ^a	0.640	0.29	8.1	0.67	335
Levobupivacaine ^b	0.560				
Ropivacaine ^c	0.727	0.52	14.0	0.48	252
Unbound concentration		F _u (%)			
- Bupivacaine ^d		3-6%			
- Ropivacaine ^e		2-6%			

^a Derived from reference 40; ^b Derived from reference 42; ^c Derived from reference 36; ^d Derived from reference 39; ^e Derived from reference 37.

Clinical efficacy after epidural anaesthesia

Ropivacaine is used clinically nowadays for central neuraxis blockade, peripheral nerve blockade and wound infiltration, although it is not registered for intrathecal use. For detailed information about perineural administration, other than epidural, the reader is referred to reviews of McClellan & Faulds⁴³ and Zink & Graf.⁴⁴

The clinical efficacy of ropivacaine after epidural administration has been compared to bupivacaine in numerous clinical trials. In general, it has been shown that onset, potency and duration of anaesthesia and analgesia of ropivacaine is comparable to that of bupivacaine.¹²

Early open studies showed that ropivacaine after epidural administration is an effective long-acting local anaesthetic in different concentrations (0.5%, 0.75% and 1.0%).⁴⁵⁻⁴⁷ Because *in vitro* and *in vivo* animal studies indicated a possible slightly decreased potency,⁴⁸⁻⁵⁰ ropivacaine has been often compared with lower concentrations of bupivacaine. Ropivacaine shows, like bupivacaine, a dose-dependent duration of sensory^{45,51,52} and motor block,^{46,53} but the duration of motor blockade seems to be shorter than with bupivacaine.^{54,55} Addition of epinephrine to ropivacaine did not result in prolonging of the sensory or motor blockade.⁵⁶ For lower limb surgery, the use of epidurally administered ropivacaine in equal^{57,58} or slightly higher concentrations^{59,60} than those of bupivacaine has shown equal efficacy for sensory and motor blockade. However, the use of higher concentrated solutions of ropivacaine (0.75% and 1.0%) may increase the clinical efficacy for this type of surgery.^{52,60} Epidural administration of ropivacaine 0.75% or 1.0% and bupivacaine 0.75% seems to be equally effective for lower gynaecological abdominal surgery,^{61,62} although motor blockade of the lower limbs may be of shorter duration and of slower onset with ropivacaine.⁶²

Ropivacaine has shown to be effective in preventing postoperative pain after major orthopaedic⁶³⁻⁶⁵ or abdominal surgery.⁶⁶⁻⁶⁸ A lesser degree of motor blockade^{64,65} and a higher percentage of patients able to mobilise early⁶⁷ were observed with ropivacaine, compared to the same or slightly reduced concentrations of bupivacaine. Addition of an opioid to a local anaesthetic, lowers the required concentration of the latter for postoperative pain, which, in turn, may decrease the risk of motor blockade.⁶⁸

Clinical potency

There has been debate about the question whether ropivacaine is less potent than bupivacaine. Studies, using an 'up-down'-sequential allocation method to determine the minimal local anaesthetic concentration (MLAC) for pain relief during labour, pointed out that ropivacaine may be less potent than bupivacaine.^{69,70} Using the same method, it was found that the minimal local anaesthetic concentration to produce motor block (MMLAC) was significantly higher for ropivacaine (0.497%) than for bupivacaine (0.326%).⁷¹ However, the clinical relevance of this method has been questioned because it compares the potency at the ED₅₀, *i.e.*, at the concentration where 50% of the patients have pain relieve and 50% have not.^{72,73} Furthermore, measurements are made at one point of the dose-response curve, which does not provide information about the shape or slope of the

dose response curve. Subsequently, no prediction can be made at the ED₉₅, which is more of clinical importance.

Vasoactivity

Several studies showed that ropivacaine is associated with concentration-dependent vasoconstrictive action on vessels, whereas bupivacaine is associated with less vasoconstrictive/more vasodilative action.^{30,31,74} Capillary blood flow,⁷⁵ as well as epidural⁷⁶ and spinal blood flow^{77,78} decreased after subcutaneous, epidural or intrathecal administration of ropivacaine in animals^{75,77,78} and humans,⁷⁶ respectively. However, intradermally injected ropivacaine showed vasoconstriction in low concentration, but not in higher concentration.⁷⁹ Furthermore, in isolated human mammary artery preparations ropivacaine showed a biphasic vasoactive effect and vasoconstriction that did not differ from lidocaine.⁸⁰ Nevertheless, it may be assumed that the vasoconstriction at low concentrations of ropivacaine is likely to contribute to its long duration of neural blockade.⁴⁴

Systemic toxicity

Evidence, as described below, suggests that ropivacaine rather than bupivacaine has a higher threshold for systemic toxicity, *i.e.*, both central nervous system (CNS) toxicity and cardiovascular (CVS) toxicity.⁴³

CNS-toxicity has been investigated in animal and human studies. Intravenous infusion of bupivacaine and ropivacaine in rats,^{81,82} as well as in healthy male volunteers demonstrated a higher tolerated dose of ropivacaine before signs of CNS-toxicity occurred.^{83,84}

CVS-toxicity of local anaesthetic may be mainly attributed to blockade of the Na⁺-channel, causing slowing of the cardiac impulse conduction.⁸⁵ An *in vitro* study demonstrated that ropivacaine blocks the cardiac Na⁺-channel in the papillary muscle of the guinea pig in a fast-in-relatively-fast-out fashion, as where bupivacaine acts in a fast-in-slow-out fashion.⁸⁶ Furthermore, blockade of cardiac K⁺-channels may contribute to the cardiotoxicity of local anaesthetics, by prolonging the action potential. The decreased potency of ropivacaine for the cardiac hKv1.5 channel, in comparison to enantiomers of bupivacaine, may partly explain its lesser cardiotoxicity.⁸⁷ In addition, ropivacaine may influence the mitochondrial energy metabolism of the heart cell less than bupivacaine, although effects on this system occurs in concentration far above those found during neural blockade.⁸⁸ All these factors may play a role in the decreased propensity to CVS-toxicity of ropivacaine.

Animal studies has shown that the lethal dose is increased for ropivacaine, in comparison to bupivacaine.⁸⁹ After deliberate overdosage of ropivacaine or bupivacaine resuscitation is more often succesful with ropivacaine.^{82,90}

The cardiotoxic effects of ropivacaine and bupivacaine after intravenous infusion have been studied clinically in healthy male volunteers. These studies showed that both ropivacaine and bupivacaine may depress myocardial conductivity, which was objectivated by changes in the electrocardiogram (ECG) and contractility, measured by Doppler echocardiography. However, QRS-widening was less with ropivacaine, compared to bupivacaine.^{83,84} In addition, bupivacaine was associated with a decreased systolic, as well as diastolic function, as where ropivacaine decreases systolic function only.⁸⁴

Levobupivacaine

Levobupivacaine (S(-)-1-butyl-2-piperidylformo-2',6'-xylidide hydrochloride) has been introduced recently. In contrast to bupivacaine, which is available as racemate, containing equal amounts of the R(+)- and S(-)-enantiomers, levobupivacaine only contains the pure S(-)-enantiomer.

Pharmacokinetics after intravenous and epidural administration

Although pharmacokinetics of levobupivacaine has been determined after intravenous infusion⁴¹ or epidural administration,^{42,91} the amount of available data on the systemic absorption and disposition is limited (Table 2 and 3). While one author reported no difference,⁹¹ another found that peak plasma concentrations of levobupivacaine were higher than those of bupivacaine after epidural administration.⁴² This is in accordance with the observations that peak plasma concentrations of S(-)-bupivacaine are higher than those of R(+)-bupivacaine after epidural administration of racemic bupivacaine.^{14,20}

Clinical efficacy after epidural anaesthesia

Levobupivacaine is used for epidural and spinal anaesthesia, as well as for peripheral nerve blockade and wound infiltration. The use of levobupivacaine is extensively reviewed by Foster & Markham,⁹² Gennery³² and McLeod & Burke.⁹³ For detailed information about perineural administration, other than epidural, the reader is refered to these reviews.

Studies, comparing levobupivacaine and bupivacaine after epidural administration show similarity in their clinical profiles. Epidurally administered levobupivacaine 0.5% and 0.75%, used for lower limb surgery, had a very similar sensory and motor blockade as bupivacaine 0.5% and 0.75%.⁹⁴⁻⁹⁶ A dose-dependent increase in the duration of sensory

blockade was observed.⁹⁴ Addition of epinephrine to levobupivacaine led to lower peak plasma concentrations and an increased rate of satisfaction of neural blockade.⁹⁷ However, variables of sensory and motor blockade did not differ between the plain solution and the solutions containing epinephrine. Levobupivacaine and bupivacaine, after epidural administration for lower abdominal surgery⁴² or caesarean section,^{91,98} showed similar clinical efficacy in concentrations of 0.75% and 0.5%, respectively. A shorter duration of analgesia was observed for levobupivacaine.⁴²

Levobupivacaine has been evaluated for continuous epidural infusion for postoperative pain.⁹⁹⁻¹⁰³ When used as the single agent, levobupivacaine 0.25% has been shown to be effective without increasing the risk of motor blockade.¹⁰² However, the addition of fentanyl,⁹⁹ morphine¹⁰⁰ or clonidine¹⁰¹ increased the clinical efficacy of postoperative epidural infusion of levobupivacaine.

Clinical potency

The MLAC of levobupivacaine (0.083%) and racemic bupivacaine (0.081%) were similar.¹⁰⁴ Furthermore, direct comparison between levobupivacaine and ropivacaine, using the same technique, showed no difference (0.087% versus 0.089%, respectively)¹⁰⁵ or a slight but insignificant difference (0.077% versus 0.092%, respectively).¹⁰⁶ Addition of fentanyl to levobupivacaine has shown to decrease the MLAC of levobupivacaine significantly.¹⁰⁷ The MMLAC of levobupivacaine (0.31%) and bupivacaine (0.27%) were significantly different, the S-enantiomer of bupivacaine being less potent.¹⁰⁸

Vasoactivity

Levobupivacaine, like racemic bupivacaine, shows a bi-phasic vasoactivity, *i.e.*, vasoconstriction in low concentrations and vasodilatation in higher concentrations. However, levobupivacaine may have a greater vasoconstrictive action than its R(+)-antipode.²⁷⁻²⁹ Although this greater vasoconstrictive action may contribute to the longer duration of neural blockade of S(-)-bupivacaine observed after intradermal injection,^{27,28} the importance of this vasoactivity on the duration of analgesia after epidural administration is not clear.

Systemic toxicity

Recent evidence, as described below, suggests that the systemic toxicity of levobupivacaine is less than that of the R(+)-bupivacaine or racemic bupivacaine.

Differences in CNS-toxicity between levobupivacaine and racemic bupivacaine has been studied in animal and humans. Symptoms of excitatory CNS-toxicity, like convulsions, occurred at a lower dose infused for bupivacaine (mean $\pm$ SD; 85 $\pm$ 11 mg) than for

levobupivacaine (103 ± 18 mg) in a sheep animal model.¹⁰⁹ There was a distinct difference in the cel firing rate in the tractus solitarius of the rat after rapid intravenous injection of S(-)-bupivacaine and R(+)-bupivacaine, the latter being the strongest inhibitor.¹¹⁰ This neuronal inhibition may be an additional factor involved in the origin of cardiotoxicity of local anaesthetics. In human volunteers, the CNS-depressant effects on the EEG were less after intravenous infusion (40 mg) of levobupivacaine than with bupivacaine in a double-blind crossover study.⁴¹

CVS-toxicity of levobupivacaine has been studied *in vitro* and in perfused organ preparations, as well as in animals and in humans. *In vitro* studies has shown that levobupivacaine may have a lower cardiotoxic potential in comparison to R(+)-bupivacaine. Valenzuela *et al.*¹¹¹ demonstrated that R(+)-bupivacaine has a higher potential than S(-)-bupivacaine for inactivated state block of the Na⁺-channel in guinea pig ventricular myocytes. Prolonged inactivated state block may extend the plateau phase of the impulse and, thereby, enhance arrhythmogenicity. S(-)-bupivacaine affected the maximal rate of depolarisation ($V_{\max}$) and action potential duration less than its R(+)-antipode in the guinea-pig papillary muscle.¹¹² Reduction of $V_{\max}$ slows the impulse conduction, which may predispose for re-entrant phenomena. R(+)-bupivacaine was more potent than S(-)-bupivacaine in blocking cardiac K⁺-channel (hKv1.5), possibly contributing to the greater cardiotoxicity observed with the R(+)-enantiomer.¹¹³ All the observed differences in blocking potential may explain the differences seen in the tendency to cardiotoxicity between levobupivacaine and R(+)- or *rac*-bupivacaine.

Perfused whole organ preparations demonstrated that S(-)-bupivacaine had less detrimental effects on the myocardium than R(+)-bupivacaine^{114,115} QRS-widening, as well as the occurrence of severe arrhythmias, were less pronounced in isolated perfused rabbit hearts receiving S(-)-bupivacaine than those receiving R(+)-bupivacaine. Atrioventricular (AV) conduction was significantly prolonged after administration of the R(+)-bupivacaine, compared to racemic and S(-)-enantiomer to isolated perfused guinea pig heart.¹¹⁵

Animal studies have been performed to determine cardiovascular changes after administration of levobupivacaine and to assess its lethal dose. The LD₅₀ was lower for the R(+)-enantiomer than for the S(-)-enantiomer of bupivacaine in small rodents after intravenous and subcutaneous administration.²² Doses of >75 mg of bupivacaine and >100 mg of levobupivacaine induced QRS widening and ventricular arrhythmias in a sheep model.¹⁰⁹ In contrast to bupivacaine, potential fatal doses of levobupivacaine (>150 mg) produced nonfatal arrhythmias that automatically returned to sinus rhythm. Mean fatal dose in sheep were higher for levobupivacaine (277 ± 51 mg) for levobupivacaine than for bupivacaine (156 ± 31 mg).¹¹⁶ Direct intracoronary injection in instrumented anaesthetized swines of bupivacaine, levobupivacaine and ropivacaine

demonstrated cardiotoxicity potency ratios, based on the lethal doses, that were 2.1:1.2:1, respectively.⁸⁹ These results may implicate that levobupivacaine is less cardiotoxic than R(+)- or *rac*-bupivacaine, but is no different from ropivacaine with regard to lethality.

Cardiovascular effects of levobupivacaine have been assessed clinically after intravenous infusion in healthy volunteers and they were compared to racemic bupivacaine.^{41,117} Focusing on inotropic effects, levobupivacaine showed less reduction in mean stroke index, acceleration index and ejection fraction than bupivacaine.¹¹⁷ Investigating differences in cardiac impulse conduction, levobupivacaine induced less prolonging of the QTc-interval on the ECG than bupivacaine.⁴¹ No other differences in ECG-changes were observed in this study.

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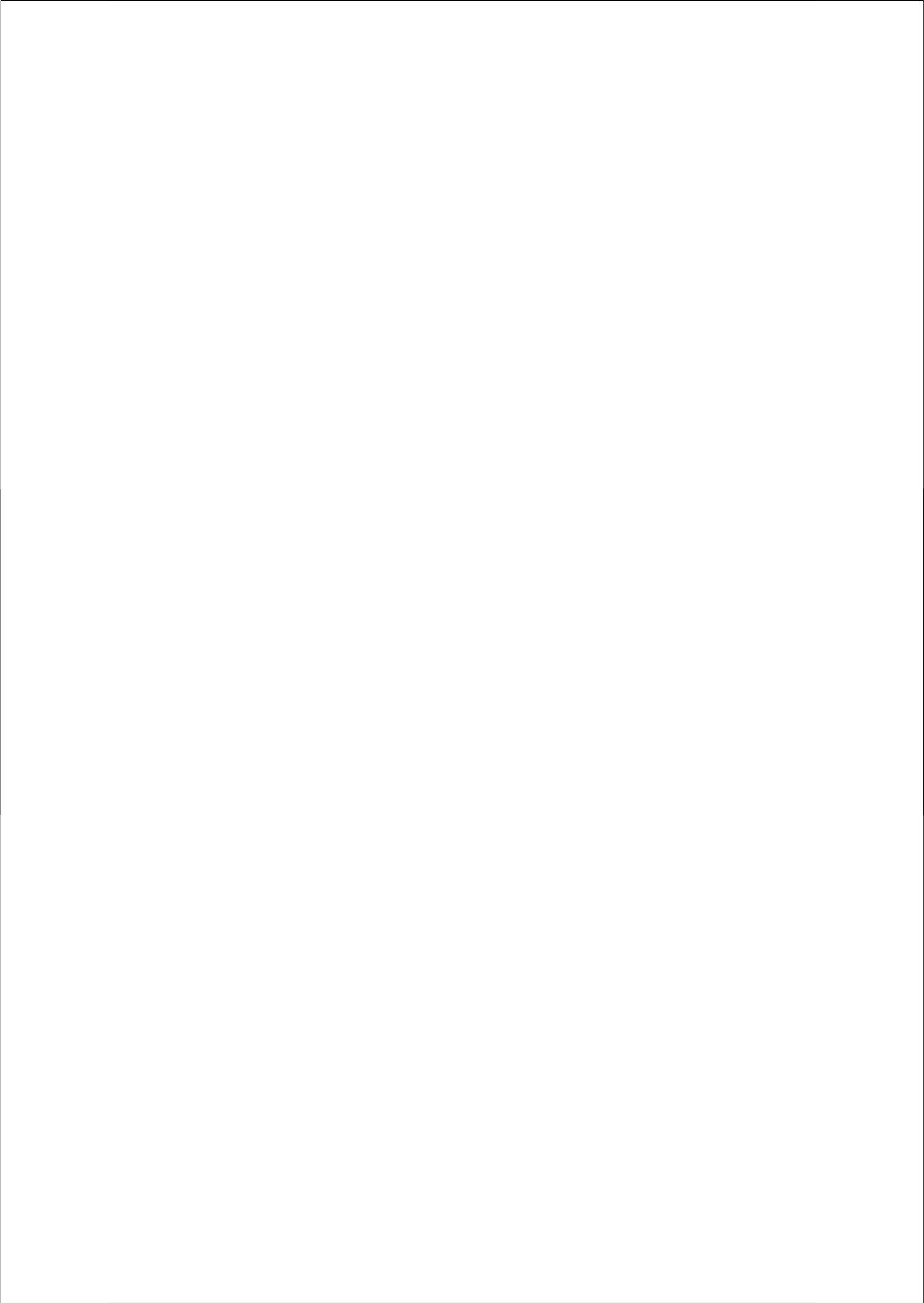
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CHAPTER 4

CIRCULATION AND EPIDURAL ANAESTHESIA

Sympathetic blockade

The cardiovascular responses to epidural anaesthesia are almost entirely due to the fact that the local anaesthetic injected into the epidural space not only blocks somatic, sensory and motor fibres, but also produces preganglionic sympathetic denervation.¹ The sympathetic trunk receives its preganglionic fibres from T1 to L2-3 (Figure 1).² The most important cardiovascular effects are related to blockade of vasoconstrictor fibres (below T4) with resulting dilatation of resistance and capacitance vessels and/or cardiac sympathetic fibres with loss of chronotropic and inotropic drive to the myocardium (T1-T5).

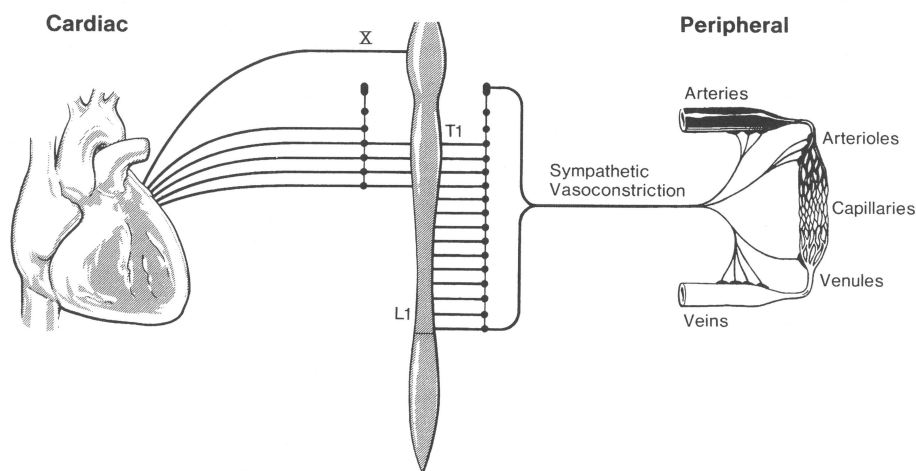


Figure 1. Sympathetic blockade: Cardiac (T1-T4) and 'peripheral' (T1-L2) sympathetic fibers are shown, as well as vagal (parasympathetic) cardiac fibers. Note the important sympathetic innervation of the arteries and venules. (Cousins MJ, Veering BT. Epidural neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural blockade in clinical anaesthesia and management of pain*. Third edition. Philadelphia, USA: Lippincott-Raven Publishers, 1998; 243-321).²

Haemodynamic changes during lumbar epidural anaesthesia

Cardiovascular effects that frequently occur after epidural administration are a decrease in arterial blood pressure and heart rate. Occasionally, profound bradycardia and even transient cardiac arrest occur during epidural anaesthesia. Several mechanisms, such as

decreased cardiac sympathetic tone, decreased venous tone, reflex decrease in heart rate resulting from decreased degree of pacemaker stretch and reflex decrease in heart rate mediated via ventricular mechanoreceptors, contribute to this phenomenon.³ The degree to which these effects occur are largely dependent on the intensity and extension of the sympathetic blockade after epidural anaesthesia.

Sympathetic blockade without involvement of the cardiac sympathetic fibres, decreases arterial vessel tone and, thus, by reducing the peripheral resistance, causes a mildly decreased systemic blood pressure. In addition, decreased tone of the venous capacitance vessels leads to the peripheral pooling of blood in the lower extremities and/or the splanchnic circulation. The capacitance of the splanchnic circulation is far greater than that of the lower extremities. As 80% of the blood volume is located in the venous system, venous dilatation influences preload of the cardiac output more than arterial dilatation.¹

Low thoracic-lumbar epidural block (T10-S5)

Low thoracic-lumbar extension of the sympathetic block (T10-S5) will cause mild reduction of the arterial blood pressure by decreasing the peripheral vascular resistance through dilatation of both the resistance and capacitance vessels of the lower limbs.⁴

Midthoracic-lumbar epidural block (T5-S5)

Extensive sympathetic blockade that includes lumbar to midthoracic spinal segments (T5-S5) is associated with more pronounced decrease in arterial blood pressure. The preganglionic sympathetic blockade results in dilatation of the splanchnic circulation, increase of the venous capacitance and decrease of the preload to the heart. Moreover, a central neural blockade extending from T6-L1 prevents stimulation of the afferent sympathetic nerves of the adrenal medulla, resulting in a reduced endogenous catecholamine secretion.

High thoracic-lumbar epidural block (>T4-S5)

Efferent sympathetic fibres to the heart, arising predominantly from the spinal levels T1-T4, control the chronotropic and inotropic cardiac drive. High thoracic segmental epidural anaesthesia (T1-T5) is associated with minimal vasodilatory effects.⁵⁻⁷ It also produces small, but significant reductions in heart rate⁷ and may slightly decrease left ventricular contractility.⁸ Extensive epidural block, involving sacral to high thoracic segments, may result in a nearly total blockade of the sympathetic outflow. This causes the blood flow to

redistribute at the expense of cardiac filling.⁹ Consequently, this may lead to substantial hypotension.

Compensation mechanisms

The effects of sympathetic blockade are, at least partially, counteracted by vasoconstriction in the remaining regions of the body that are not sympathetically denervated after epidural blockade (Figure 2).^{10,11} Besides that, an increase in heart rate will compensate the decrease in preload after sympathetic blockade.¹² Sympathetic blockade after epidural anaesthesia seems to be incomplete.¹³ Therefore, preganglionic sympathetic fibres innervating the adrenal medulla and innervating sympathetic fibres could be activated even after quite extensive blockade to C8, in reaction to decreased blood pressure.¹³

Haemodynamic changes in the elderly during epidural anaesthesia

Hypotension and bradycardia are the most common adverse effects of central neuraxis blockade.^{14,15} High levels of anaesthesia are associated with a decrease in arterial blood pressure, after epidural,¹⁴ as well as subarachnoid blockade.^{16,17} Furthermore, old age is associated with a higher risk of developing hypotension after spinal anaesthesia. In older patients, hypotension occurs with an incidence of 15.3% to 33% after subarachnoid blockade.^{16,17} The incidence of hypotension during epidural anaesthesia has been studied less frequently, but has been reported to be 11%-15%.^{14,18} Until now, few studies have been performed on the influence of age on the incidence of hypotension and bradycardia after epidural anaesthesia. However, the incidence of hypotension may be higher in older patients. Wolf *et al.*¹⁹ studied an older group of patients (mean age 60-65 yr) to determine the effects of epidurally administered ropivacaine. They found an incidence of hypotension, requiring treatment, of 48%, 70% and 100% after administering 20 ml of ropivacaine 0.5%, 0.75% and 1.0%, respectively.

Bradycardia after spinal anaesthesia occurs in 10%-13% of the patients. It is associated with a high level of sensory blockade ($\geq$ Th 5-6), but not with old age.^{16,17} Bradycardia after epidural anaesthesia occurs in 2%-14%,^{14,18} but a higher incidence upto 47% has been found in a population of old patients with median cephalad levels of analgesia of T4.¹⁹ This may be partly caused by the involvement of cardiac sympathetic fibers. The possible effects of age on cardiovascular changes after epidural anaesthesia are described in more detail in Chapter 5.

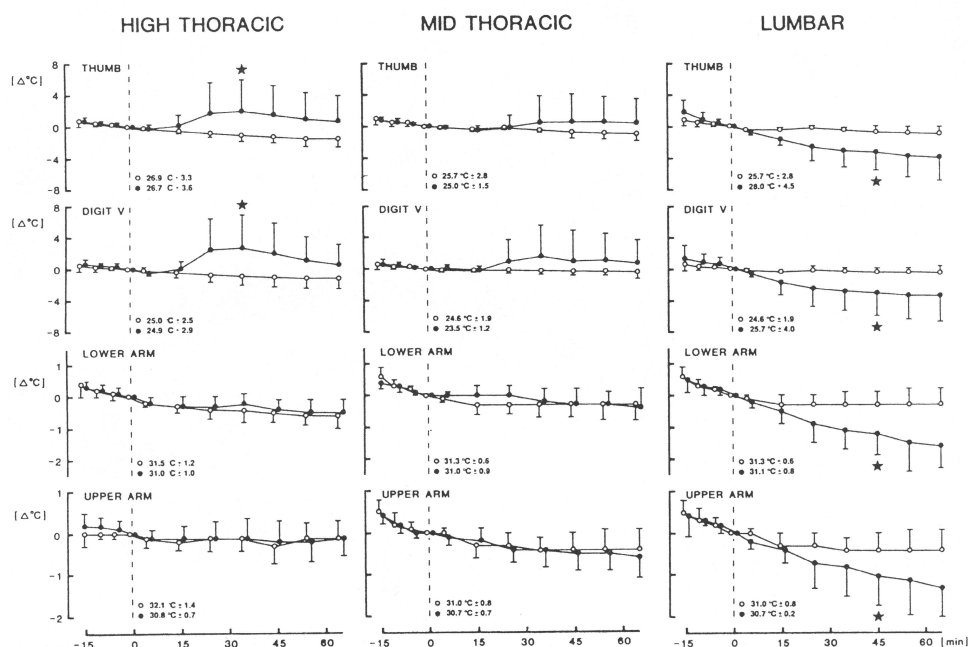


Figure 2. Changes in upper limb skin temperatures from baseline with high thoracic, midthoracic and lumbar epidural injection of either bupivacaine (filled symbols) or saline (open symbols). With high thoracic epidural anaesthesia the skin temperature on the hand, *i.e.*, on the thumb and on digit 5, increased significantly, suggesting sympathetic blockade in the upper limb. In contrast, with lumbar epidural anaesthesia, finger, lower and upper arm skin temperature decreased significantly, suggesting compensatory vasoconstriction in the upper limb (Hopf *et al. Anaesthesiology* 1990; 73: 882-889).¹¹

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CHAPTER 5

AGE-RELATED FACTORS AND EFFECTS IN RELATION TO EPIDURAL ANAESTHESIA

Process of ageing

Elderly patients should be viewed from the perspective of understanding ageing, how it occurs, how it affects specific organ systems and how it may influence peri-operative care when a patient is subjected to surgery. Ageing is a normal phenomenon, although the basic mechanisms that cause ageing are still poorly understood. Ageing per se is represented by those manifestations of irreversibly altered organ function that are common in all elderly persons and are usually progressive. The physiological process of ageing varies considerable from person to person; hence variation in organ capabilities increases with age. Different organs in the same individual may age at different rates: each system has its own temporal pattern of age change.¹ The organ reserves, essential to ensure homeostasis, gradually decrease. This results in an increased sensitivity to internal and external environmental stressful stimuli (Figure 1).¹ However, physiological ageing can be influenced by external influences such as cigarette smoking, physical activity, nutrition intake and socio-economic status.^{1,2}

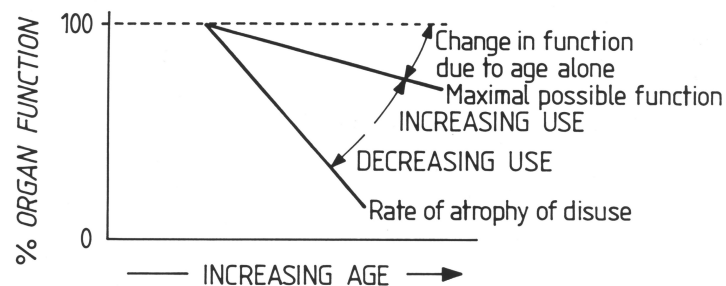


Figure 1. The decline in organ function, influenced by ageing. The upper curve represents the maximal possible performance of a given organ system, whereas the lower curve shows the rate of atrophy when the system is never stressed. Organ function always occurs at some point between the two curves. The slope of the upper curve defines the change in function resulting from ageing (Williams ME. *Am J Med* 1984; 76: 1049-54).¹

Demographics of ageing

The world's elderly population (defined as being 65 years of age and older) is still growing in the developed countries, as well as in the developing countries (Figure 2). Europe has had the highest proportion of population aged 65 and over and it is expected that it will continue to be in the lead in that respect in the twenty-first century.³ In Europe, the proportion of the population older than 65 years is expected to rise from 15.5% in

2000 to 24.3% in 2030. In addition, the “oldest old” (people aged 80 and over) are the fastest growing segment of the total population, with estimated growths of $\pm 6\%$ in 2000 to 10% in 2030 in Europe and North America. Nowadays, an increased number of surgical procedures, which are often more complex to carry out, are performed in the elderly due to progress in management and surgical techniques.^{4,5} It is conceivable that the percentage of elderly people that are presented to undergo surgery under anaesthesia will continue to grow. A French survey investigating the changes in the French practice of anaesthesia, demonstrated an age-dependent increase in the annual rate of anaesthetics ($>25\%$ at the age of 65 years and older).⁶ In addition, a Swiss study showed that the increase in anaesthetic workload over a ten-years period could be attributed to the increased number of elderly patients undergoing anaesthesia.⁷

Average Annual Percent Growth of Elderly Population in Developed and Developing Countries

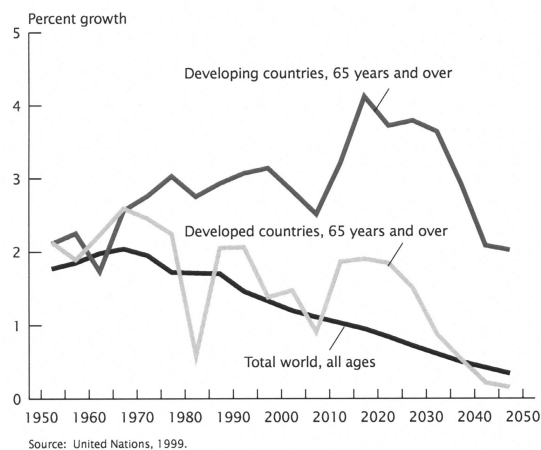


Figure 2. Average annual percent growth of elderly population in developed and developing countries (Kinsella K, Velkoff VA. *An Aging World: 2001*. U.S. Census Bureau. Washington, DC: U.S. Government Printing Office, 2001).⁵

Age-related factors contributing to the haemodynamic effects of epidural anaesthesia

Effective interaction between both the cardiovascular and autonomic nervous system is necessary to compensate for the potential haemodynamic destabilizing effects of general anaesthesia, as well as central neural blockade.² One of the objectives of anaesthesia is to maintain haemodynamic stability during surgery. However, the achievement of this goal

can be seriously hampered by the influence of age on the cardiovascular and autonomic nervous system. The most significant changes with age are stiffening of the components of the cardiovascular system, decreased beta-adrenoreceptor responsiveness and increased sympathetic nervous system activity.⁸

Cardiovascular system

Vessels

Wall thickening, particularly intimal thickening, and dilatation are the main structural changes that occur within large elastic arteries during ageing.⁹ Structural changes in the media layer of the vessels consist of increased collagen content, covalent cross-linking of collagen, reduced elastin content, elastin fracture and calcification.^{2,8} Alterations in endothelial function are to be expected at about the 6th decade of life. All these processes lead to an increase in vessel stiffness and reduction in arterial compliance. Whereas in younger subjects the blood pressure is primarily regulated by the peripheral vascular resistance, in older persons this is determined mainly by the stiffness of the large central vessels. As a result, increased age is associated with an increased systolic blood pressure, decreased diastolic blood pressure and an increased pulse pressure.¹⁰

Heart

Changes in cardiac morphology reflect numerous changes that occur with age at the molecular level in the heart. Structural changes include decrease in the number of myocytes, increases in myocyte size, increases in left ventricular wall thickness, decreases in conduction fibre density and decreases in sinus node cell number.¹¹ Sequentially, these alterations influence the cardiac function in response to increasing stimulation. Hypertrophy of the left ventricular wall in response to the chronically increased afterload, is caused by the early reflected pulse pressure wave and late peak systolic pressure, associated with the increased arterial vascular stiffness.^{2,8,9} Left ventricular hypertrophy prolongs myocardial contraction, maintaining the left ventricular ejection fraction (Table 1).² However, it delays ventricular relaxation, which impairs the early diastolic filling rate. The age-related increase in stiffness of the left ventricle causes the cardiac function to be more dependent on ventricular filling.^{12,13} The end-diastolic pressure, required to have adequate filling of the ventricles, are shifted upward in comparison to younger subjects (Figure 3).⁸ Furthermore, the stroke volume remains unchanged with exercise, but the increase in ejection fraction is blunted because the older heart fails to empty as completely as in the younger heart (Table 2).² Cardiac reserve decreases with increasing age and is further influenced by concomitant cardiac disease. Therefore, the increase in cardiac output as a reaction on stress or exercise is reduced.

Table 1. Changes in cardiac output regulation in healthy people between 20 and 80 years of age when in rest and seated (Lakatta EG. *J Am Geriatr Soc* 1999; 47: 613-25).²

Parameter	Change
Cardiac Index	No change [‡]
Heart Rate	Decreased (10%)
Stroke volume	Increased (10%)
Preload EDV	Increased (12%) [†]
Preload Early filling	Decreased
Preload Late filling	Increased
Afterload Compliance	Decreased
Afterload Reflected waves	Increased
Afterload PVR	No change [*]
Contractility	No change
Ejection Fraction	No change
LV-mass	Increased

[‡] Decreased with age in women; [†] unchanged with age in women; ^{*} Increased with age in women; EDV=end diastolic volume; PVR=peripheral vascular resistance

Table 2. Changes in cardiac regulation in healthy men and women between 20 and 80 years of age at exhaustive upright exercise (Lakatta EG. *J Am Geriatr Soc* 1999; 47: 613-25).²

Parameter	Change
Cardiac Index	Decreased (25%)
Heart Rate	Decreased (25%)
Stroke volume	No change
Preload EDV	Increased (30%)
Afterload Vascular (PVR)	Increased (30%)
Afterload Cardiac (ESV)	Increased (275%)
Contractility	Decreased (60%)
Ejection fraction	Decreased (15%)
Plasma catecholamines	Increased
Cardiac and vascular responses to β -adrenergic stimulation	Decreased

EDV=end diastolic volume; PVR=peripheral vascular resistance; ESV=end systolic volume

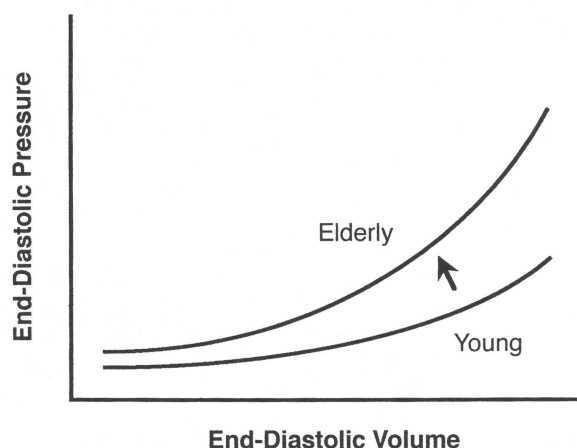


Figure 3. Aging is associated with increased cardiac stiffness. Left atrial pressure must therefore be higher in order to achieve the same end-diastolic volume in the older ventricle as in the young ventricle (Rooke GA, Robinson BJ. Properties, cardiovascular and autonomic aging. In: Fleisher L, Prough D. eds. *Problems in anesthesia: Management of the elderly surgical patient*. Vol. 9. Philadelphia, USA: Lippincott-Raven Publishers, 1995; 482-497).⁸

Autonomic nervous system and baroreceptor reflex

Autonomic nervous system

One of the most striking effects of age is a decrease in the response to beta-adrenoreceptor stimulation with increasing age, which results in a functional cardiac beta-receptor blockade.^{8,14,15} This desensitisation may be the consequence of changes in the affinity of the beta-adrenoreceptor for beta-adrenergic agonists or in the efficacy of post-receptor coupling to the intracellular signalling pathways, rather than to the loss of beta-adrenoreceptors.²

Ageing causes an 'hyperadrenergic state',¹⁶ which is demonstrated by an increased sympathetic outflow,¹⁷ as well as higher plasma concentrations of norepinephrine in the elderly.¹⁸⁻²⁰ Parasympathetic cardiac control seems to be decreased in the elderly.²¹

Baroreceptor reflex

The baroreflex is an important mechanism for rapid haemodynamic homeostasis. Studies from the 1970s showed an age-related decline in baroreflex sensitivity, but it was unclear whether the age-related increase in blood pressure could account for this effect.²²

A recent study found that age as well as an elevated systolic blood pressure were associated with a non-linear decline in baroreflex sensitivity. Although age was the strongest predictor of variability in the model, little changes occurred after the fourth decade of age.²³ Others^{2,8} suggested that there is little evidence that ageing has a significant effect on the nervous system components of the baroreflex, but that the decline of the baroreflex sensitivity emerges from the relative unresponsiveness of peripheral end-organs to beta-adrenergic stimulation or from impairment of the parasympathetic component of the arterial baroreflex.^{17,21}

Response to sympathetic blockade associated with epidural anaesthesia in the elderly patient

Decreased cardiac reserve, structural changes in the heart and arterioles, and changes in the autonomic nervous system with increasing age may contribute to substantial hypotension in elderly patients after central neural blockade. With advancing age, compensation mechanisms may be less than optimal. Elderly patients may have a reduced baroreceptor-mediated response of the heart rate on exercise and stress.²⁴

The diminished elasticity and fibrotic changes of the heart muscle make the aged heart non-compliant and thus both volume-sensitive and volume-intolerant. Elderly patients appear to be more often hypovolaemic upon arrival at the operating room.⁸ Preload with crystalloids or colloids fluids may compensate for fluid deficits as well as for the dilatation of the venous system.²⁵ However, preloading has been shown not always to be effective in older patients.^{26,27} Rapid volume preloading constitutes a potential risk in older patients with limited cardiac reserve. Furthermore, when the central neural blockade regresses, it causes redistribution of fluids from the third space to the central circulation, possibly putting the older patient at risk for fluid overloading. A combination of the administration of about 7 ml.kg⁻¹ colloid preload and the use of an α -agonist during the induction phase has been recommended to compensate for the decrease in central venous pressure and vascular resistance, respectively.²⁸

Baroreflex regulation of sympathetic vasoconstrictor outflow is not impaired with increasing age.^{17,29} Thus, compensatory vasoconstriction above the spinal level of sympathetic blockade after epidural anaesthesia may counteract the vasodilatory effects below that level in elderly patients to the same extent as in younger people.

Age-related factors contributing to the pharmacokinetics and clinical characteristics of epidural anaesthesia

Anatomical and physiological changes, associated with increasing age, may affect the clinical characteristics and the pharmacokinetics after epidural administration of a local anaesthetic (figure 4).

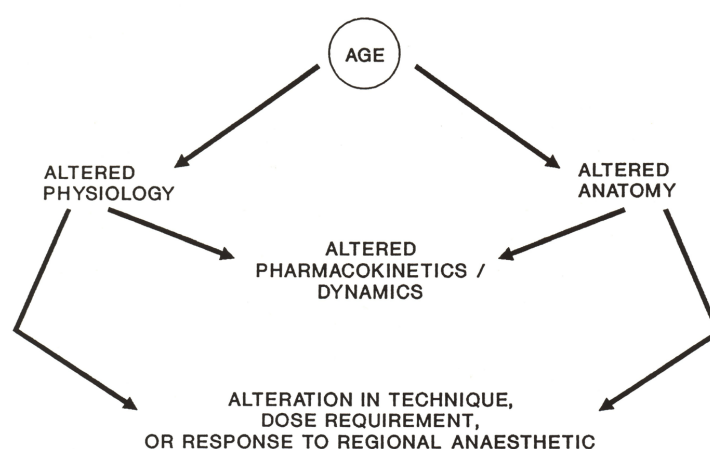


Figure 4. Factors which can modify central neuraxis blockade in the elderly patients (Veering BT. *Epidural and spinal anaesthesia with bupivacaine: Neural blockade and pharmacokinetics.* Thesis, 1991, Leiden).

Age-related factors influencing the pharmacokinetics after epidural anaesthesia

Changes in body composition, drug binding, hepatic blood flow and hepatic mass that occur with normal ageing may have an impact on the rate and extent of the systemic absorption, distribution, metabolism and excretion of local anaesthetics.

Systemic absorption

The absorption rate of local anaesthetics is primarily dependent upon local blood flow at the site of injection and upon binding to local tissues. Age-related changes in either local blood flow and/or composition of the contents of the epidural space may influence the systemic absorption of local anaesthetics.

Systemic disposition

Increasing age is associated with an increase in body fat, reduced mean body mass and a decrease in total body water.^{30,31} These changes may increase the volume of distribution of lipophilic local anaesthetics. Although this has been demonstrated for lidocaine in one study,³² other authors found an unchanged volume of distribution.^{33,34}

Differences in plasma protein concentration or binding between young and old patients could possibly influence the distribution of the local anaesthetic agents. However, the significance of plasma binding as a determinant of the overall distribution is limited due to the extensive tissue uptake of local anaesthetics.³⁵ It has been shown that the concentration of α_1 -acid glycoprotein (AAG), the most important protein to which local anaesthetics bind, did not change with age (Figure 5).³⁶ The plasma protein binding of bupivacaine did not change with increasing age (Figure 6),³⁷ whereas the binding of lidocaine tended to increase.^{34,38}

Local anaesthetics are primarily eliminated by metabolism. For amide-type local anaesthetics this occurs predominantly in the liver. Older patients exhibit a declined hepatic blood flow and a reduced hepatic mass.³⁹⁻⁴¹ The decline in hepatic blood flow with increasing age may influence the clearance of local anaesthetics with a high hepatic extraction ratio. This has been confirmed for lidocaine.⁴²

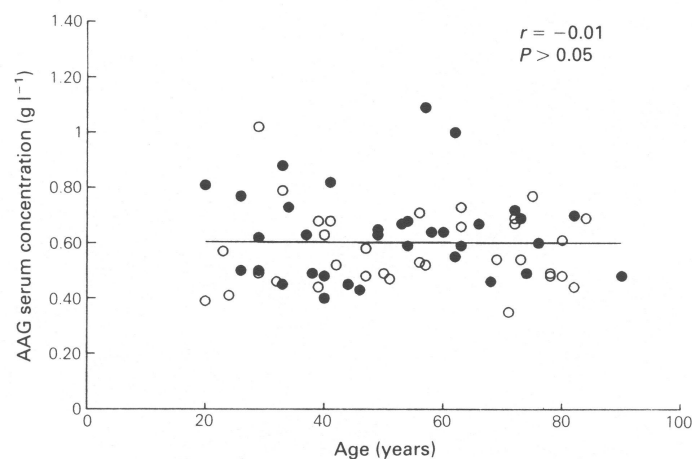


Figure 5. Effects of age on the serum concentration of AAG in 35 male and 35 female subjects (Veering *et al. Br J Clin Pharmacol* 1990; 29: 201-6).

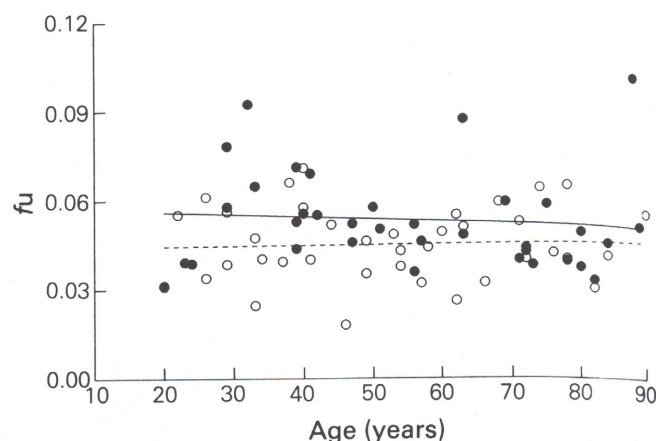


Figure 6. The relationship between age and the free fraction of bupivacaine in serum in 39 male and 35 female subjects (Veering *et al. Br J Clin Pharmacol* 1991; 32: 501-3).

The elimination of local anaesthetics with a relatively low hepatic extraction ratio, like bupivacaine and ropivacaine, primarily depends upon hepatic enzyme-activity and plasma protein binding. An age-dependent decrease in clearance of these local anaesthetics is associated with a reduced hepatic mass, but it is controversial whether the intrinsic clearance of drugs is deficient in older patients. The *in vitro* activity of most of the microsomal mono-oxygenases in the human liver has been shown not to be influenced greatly by age.⁴³

Thus, the decreased clearance of local anaesthetics is associated with a decline in hepatic blood flow and reduced liver mass, but, until now, cannot be explained by an age-related reduction in intrinsic hepatic enzymatic activity nor by differences in plasma protein binding.

Age-related factors influencing the clinical course of epidural anaesthesia

Starting from the age of 20, the number of myelinated fibres in the dorsal and ventral roots declines to one third at the age of 90.⁴⁴ Deterioration of myelin sheaths and structural changes in the dura mater, as well as changes in the ground substances may increase permeability in the elderly.^{45,46} These changes may result in changes in local distribution, *i.e.*, in the distribution rate of the local anaesthetic from the site of injection to the sites of action and may account for the increased sensitivity for local anaesthetics seen in the elderly. With age, the number of axons in peripheral nerves diminishes and the conduction velocity, particularly in motor nerves, is slowed.^{47,48} These factors may all contribute to the effects of age on central neural blockade.

Anatomic changes, like sclerosis and calcification of the intervertebral foramina are likely to reduce the paravertebral spread of local anaesthetic.^{44,49-51} A reduced fatty tissue content of the epidural space with increasing age may contribute to a more compliant and less resistant extradural space.^{52,53} These mechanisms may partially explain the extended longitudinal spread, associated with increasing age.^{49,54} Furthermore, continuing osteoarthritic degeneration and cartilage calcification change the anatomical configuration of the lumbar and thoracic spine.⁴⁴ These changes could reduce the epidural space, thereby influencing the pattern of spread of the local anaesthetic.

The site of action of an epidurally administered local anaesthetic may shift from a predominantly paravertebral in the young to a subdural or transdural site in the elderly.^{44,49} For local anaesthetics, this may be caused by an increased permeability of the dura mater, probably due to an increase in size of the arachnoid villi.⁵⁵

All abovementioned factors may contribute to an increased sensitivity to local anaesthetics in elderly patients.⁵⁶

The effects of age on pharmacokinetics of local anaesthetics following central neural blockade

The effects of age on the systemic absorption

After epidural and caudal administration the peak plasma concentration of lidocaine did not differ between young and old patients.⁵⁷⁻⁵⁹ Veering *et al.*^{60,61} investigated the effects of age on the systemic absorption of bupivacaine after epidural and subarachnoid administration. Age did not influence the initial absorption after epidural and subarachnoid administration. However, the mean absorption rate was shorter after subarachnoid administration, because of a faster late absorption rate in the elderly patients.⁶⁰ Consequently, a shorter absorption time would be expected to shorten the duration of spinal analgesia in the elderly, but this has not been demonstrated.

The effects of age on the systemic disposition

After epidural administration, total plasma clearance of lidocaine has been shown to be decreased in older patients.⁶² In addition, total plasma clearance of bupivacaine was decreased after epidural,⁶³ as well after subarachnoid administration (Figure 7).^{60,64,65} Prolonged epidural infusion of racemic bupivacaine in an elderly population showed that unbound plasma concentrations did not increase over time, despite of increasing total

plasma concentrations.⁶⁶ This may be the result of increased protein-binding, secondary to an increased concentration of α_1 -acid glycoprotein postoperatively. Age-related stereoselective differences in intrinsic hepatic clearance may theoretically lead to an increase of the concentration of one enantiomer, compared to the other after administration of a racemic mixture.^{41,67} However, the ratio of the total, as well as the unbound fraction of the S(-)- and R(+)-enantiomer of bupivacaine, remained constant during the 48-hours of epidural infusion in the abovementioned aged population.⁶⁶

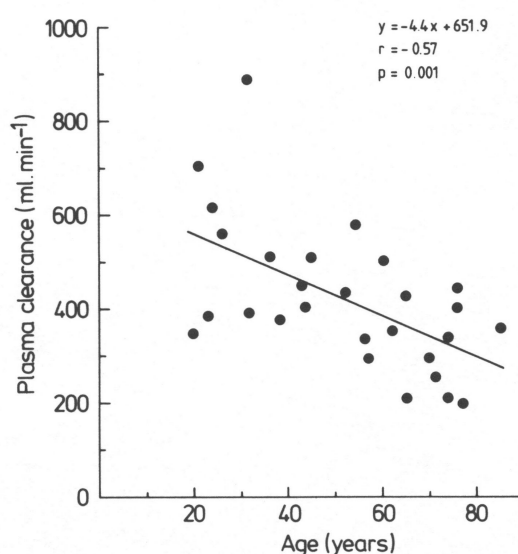


Figure 7. Relationship between total plasma clearance and age (Veering *et al. Anesth Analg* 1987; 66: 589-93).

The effects of age on sensory and motor blockade of local anaesthetics following central neural blockade

Increased age is generally associated with an increase in the spread of analgesia after epidural administration.^{61,63,68-73} However, discrepancy exists among different studies and some authors did not find a correlation between age and spread of analgesia after epidural or caudal anaesthesia.^{57,74} Furthermore, there is a considerable variability in the spread of analgesia between persons of the same age.^{69,71}

Bromage⁶⁸ used a variable amount of local anaesthetic to calculate the epidural segmental dose requirements (ESDR). The ESDR, expressed in dose per spinal segment to be blocked, rose steeply until the age of 18.5 years and then declined slowly with age. However, the validation of this method has been questioned because it assumes a linear dose response between the number of segments blocked and the amount of local anaesthetic administered to the patient.⁶⁹⁻⁷¹ It has been shown that for older patients the ESDR is a dependent variable of the volume injected, meaning that to block an additional spinal segment, a larger dose of local anaesthetic per segment is required.⁷⁰

Other authors have used a fixed epidural dose of local anaesthetic to study the effects of age on the sensory spread.^{69,71,72} Advancing age was associated with increased highest level of analgesia. Wolff *et al.*⁷⁵ studying epidural anaesthesia with ropivacaine in different concentrations (0.5%, 0.75% and 1.0%) in a cohort of elderly patients (mean age >60 years) reported high levels of anaesthesia (T4) with all concentrations.

In our institution the effects of age on the sensory and motor blockade have been investigated after epidural administration of a fixed amount of a solution of bupivacaine.^{61,63} These studies confirmed that the highest level of analgesia increased with age (Figure 8). Furthermore, the elderly patients had a faster onset of analgesia at the caudad segments (Figure 9)^{61,63} and the rate of regression was prolonged.⁶¹ Time until total recovery of the sensory block was, however, not affected by age.^{61,63} The intensity of motor blockade was enhanced and the onset was faster in the eldest compared to the youngest patients.⁶¹

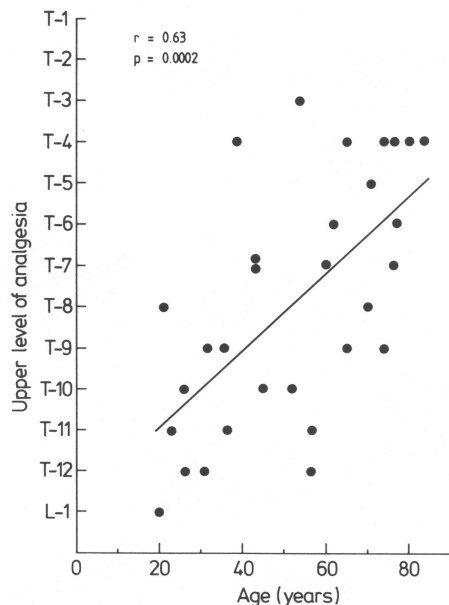


Figure 8. Relationship between the upper level of analgesia and age after epidural administration of bupivacaine 0.5% (Veering *et al. Anesth Analg* 1987; 66: 589-93).

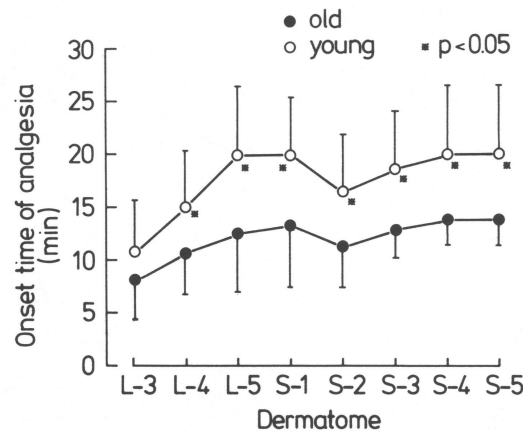


Figure 9. Mean onset times of the caudad segments in the young and old patient groups after epidural administration of bupivacaine 0.5% (Veering *et al. Anesth Analg* 1987; 66: 589-93).

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CHAPTER 6

AIMS AND DESIGN OF THE STUDIES

Main objectives

The first objective of the investigations described in this thesis was to provide a detailed description of the pharmacokinetics, in particular of the absorption, after epidural administration of the novel local anaesthetics levobupivacaine and ropivacaine. The second objective was to assess the influence of age on the systemic absorption and systemic distribution, as well as on the neural blockade (sensory and motor blockade) and haemodynamic changes after epidural anaesthesia with levobupivacaine and ropivacaine. Finally, the third objective was pharmacokinetic/ pharmacodynamic (PK/PD-) modelling of epidural anaesthesia with bupivacaine, levobupivacaine and ropivacaine. Covariates, such as the local anaesthetic, age, height and weight will be incorporated in this model.

Introduction

Chapter 1 reviews the anatomy and physiology of the epidural and subarachnoid spaces in relation to lumbar epidural anaesthesia, which is the subject of our studies.

Chapter 2 summarizes the mechanisms and sites of action of epidurally administered local anaesthetics. Furthermore, the pharmacokinetics of local anaesthetics after central neuraxis blockade are discussed.

Chapter 3 provides a definition of chirality and the nomenclature of enantiomers. It outlines the differences between enantiomers of local anaesthetics with regard to pharmacokinetics and nerve blocking characteristics. In addition, two enantiomerically pure local anaesthetic agents, used in our studies, are discussed.

Chapter 4 describes the haemodynamic changes that result from preganglionic sympathetic denervation after epidural blockade, and the counteracting compensation mechanisms. It will focus particularly on the haemodynamic changes in elderly people.

Chapter 5 provides both a description of the process of ageing, as well as the demographics of ageing. In addition, possible age-related factors and the effects of age on the haemodynamic response, the pharmacokinetics and the sensory and motor blockade after epidural anaesthesia are discussed, as far as this has been investigated in earlier studies.

Clinical effects & pharmacokinetics

Anatomical and physiological changes may influence the systemic absorption and disposition and the clinical course after epidural administration of local anaesthetics. Furthermore, detailed knowledge of both the systemic absorption and disposition of a local anaesthetic after perineural administration is essential with regard to the clinical profile and the risk of systemic toxicity.

Pharmacokinetics have been obtained for lidocaine and bupivacaine, using a stable-isotope method. This approach allows simultaneous determination of the absorption and disposition kinetics. The equivalence of levobupivacaine and its deuterium-labelled counterpart, which is a precondition for the use of this method to evaluate the pharmacokinetics of levobupivacaine, is described in Chapter 7. Subsequently, the pharmacokinetics of the new enantiomerically pure local anaesthetics levobupivacaine and ropivacaine are investigated and described in Chapter 8 to 10.

The effects of age on the sensory and motor blockade, as well on the pharmacokinetics after epidural anaesthesia with bupivacaine have been investigated. Elderly patients displayed a larger spread of anaesthesia and an enhanced motor blockade. In addition, age influenced the disposition kinetics, especially the total plasma clearance, but not the absorption kinetics of bupivacaine. The studies, described in Chapter 9 to 11, investigate the effects of age on the pharmacokinetics and clinical course after epidural administration of the novel local anaesthetics levobupivacaine and ropivacaine, respectively.

Haemodynamic effects

Changes in the cardiovascular and autonomic nervous system with increasing age may contribute to an altered haemodynamic response to epidural anaesthesia. The study, described in Chapter 11, compares the haemodynamic effects in age groups after epidural administration of ropivacaine 1.0%. Next to the effects on blood pressure and heart rate, epidural anaesthesia may influence the cardiac output and hepatic blood flow, potentially altering the clearance of drugs. The study, described in Chapter 12 investigates the influences of age and the level of analgesia on the haemodynamic parameters, including cardiac output and the influence of age on liver blood flow after intravenous infusion of a colloid solution and after induction of epidural anaesthesia. In this study cardiac output and liver blood flow are determined using non-invasive pulse dye densitometry of indocyanine green (ICG).

Modelling

In the past 20 years, different investigators in our institution have determined the absorption kinetics of several local anaesthetics under very similar circumstances, using the stable-isotope method. Simultaneously to the collection of these pharmacokinetic data, neural blockade characteristics of individual patients were recorded. Absorption data obtained for bupivacaine, ropivacaine and levobupivacaine are collected to derive population pharmacokinetics, using NONMEM. The next step is to construct a pharmacokinetic/pharmacodynamic (PK/PD-) model, by which the probability of sensory block at each dermatome level can be estimated from the absorption data. The covariates, entered in this model, are the local anaesthetic agent, age, length and weight. The influence of these factors on the spread and duration of analgesia are estimated.

Conclusions and Perspectives

Chapter 14 summarises the results of the investigations that are subject of this thesis. In addition, suggestions for future studies are provided.