Rational use of antibiotics

Dijkmans, A.C.

CHAPTER 2

A SIMPLIFIED ORAL FLUCLOXACILLIN ABSORPTION TEST FOR PATIENTS REQUIRING LONG-TERM TREATMENT

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Dijkmans AC,[1,2] den Hartigh J,[2] van Dissel JT,[2] Burggraaf J[1,2]

1 Centre for Human Drug Research, Leiden, The Netherlands
2 Leiden University Medical Center, Leiden, The Netherlands

ABSTRACT

BACKGROUND Patients with severe methicillin-sensitive *Staphylococcus aureus* infections are effectively treated with initial continuous intravenous (IV) flucloxacillin followed by oral maintenance therapy. As the absorption of oral flucloxacillin is variable, an oral absorption test (OAT) is used to ensure efficacious therapy. The classical OAT (test A) requires overnight fasting, interruption of IV therapy, and is laborious. We designed a simplified OAT (test B) in which IV therapy is continued and oral dosing is performed after a 1-hour fast.

METHODS In 43 hospitalized patients on IV flucloxacillin, either test A or test B was performed. In each variant, 1g of oral flucloxacillin was given, and blood samples were taken before and at 1 and 2 hours after dosing. Flucloxacillin concentration was determined by high-performance liquid chromatography. Adequate absorption was defined as a 10 mg/l increase in flucloxacillin concentration at 1 or 2 hours after dosing.

RESULTS In a population of 43 patients (18F/25M), test A was done in 19 patients and test B in 24 patients. The groups had similar baseline characteristics such as age, renal function, gender, diagnoses, or comedication. All the patients tolerated the test without problems. The absorption was highly variable between patients. The average (SD; range) maximal increase for test A was 22.3 (11.6; 7–50) mg/l and 26.5 (12.6; 8–53) mg/l for test B. There was no significant difference between the 2 tests (p=0.23), and 10% of the patients were poor absorbers (increase <10 mg/l). There was no influence of serum creatinine, age, or pretest flucloxacillin concentration. No clinical condition or drug use that may have impaired flucloxacillin absorption could be identified.

CONCLUSIONS We designed a simplified OAT that performs well and can be implemented easily. This test may be helpful to rationally and effectively treat patients with severe methicillin-sensitive *S. aureus* infections with an orally administered small-spectrum antibiotic.

INTRODUCTION

Staphylococcus aureus is a pathogen responsible for infections of different severity.[1] Severe infections are increasing worldwide, mostly due to the increasing use of indwelling catheters, vascular and orthopedic prostheses, and prosthetic heart valves. The treatment of choice for these severe infections is dependent on the susceptibility pattern of the pathogen, the country-specific prevalence of methicillin-resistant *S. aureus* (MRSA) strains and physician preference. In low endemic MRSA countries such as the Nordic countries, the Baltic states, and The Netherlands,[2] the preferred and efficacious treatment consists of initial continuous intravenous (IV) flucloxacillin followed by oral flucloxacillin for a variable period of time. The advantages of the latter treatment option are the bactericidal properties of the penicillin, its small-spectrum, the low costs, and the possibility to switch to oral dosing as soon as possible, allowing early discharge of the patient. The pharmacokinetics of oral flucloxacillin is characterized by a rapid absorption with maximal concentrations at approximately 1 hour, 90% protein binding, and an elimination half-life of 1 hour. However, the amount of flucloxacillin absorbed after oral administration is highly variable.[3] The reasons for the variability are largely unknown and likely related to factors such as gastrointestinal motility as there is no published data suggesting involvement of (genetic) variability in drug transporter expression or function. Thus, the preferred therapeutic approach ideally requires assessment of the efficacy of oral absorption of flucloxacillin. The criterion for adequate absorption can be derived from the full pharmacokinetic profile of flucloxacillin and the minimum inhibitory concentration (MIC) of the isolate. The breakpoint MIC for flucloxacillin-susceptible *S. aureus*, defined as the highest MIC value still to be interpreted as indicating susceptibility, is commonly <0.5 mg/l of free drug and translates into a total drug concentration of 5 mg/l. Therefore, we routinely accept flucloxacillin concentration of at least 10 mg/l. This results in free drug concentrations >1 mg/l, which is well above the MIC for most strains.

As the elimination half-life of flucloxacillin is 1 hour, it can be calculated that with a daily dose regimen of at least 5 times 1g of oral flucloxacillin, concentrations will be above the MIC for at least 60% of the dosing interval, which is the generally accepted exposure goal to achieve efficacious treatment of susceptible *S. aureus* strains by beta-lactam antibiotics.[4] Indeed, the oral absorption test (OAT) routinely performed in our institution shows that approximately 10% of the patients do not absorb well enough, for example, have a maximal concentration <10 mg/l. The disadvantages of the test in its current format are that it requires cessation of the continuous IV administration and that it is laborious. We hypothesized that a simpler test with continuation of the IV therapy would perform equally well and can be used routinely in clinical practice at low costs.

PATIENTS AND METHODS

This trial complied with institutional guidelines and Dutch law as the evaluation concerned daily routine practice that subsides under the law on the medical treatment agreement (WGBO; Wet op de Geneeskundige Behandelings Overeenkomst). Hence, separate medical ethical approval was not needed.

PATIENTS

The evaluation period included patients admitted in 2009 and 2010 to Leiden University Medical Center, Leiden, The Netherlands. Data were collected from 43 hospitalized patients with the only inclusion criteria that they received initial continuous IV flucloxacillin and were scheduled for maintenance treatment with oral flucloxacillin. No potentially eligible patients were excluded from the evaluation.

FLUCLOXACILLIN ORAL ABSORPTION TESTS

We evaluated 2 different test protocols to assess the oral absorption of flucloxacillin. The first test (test A) started with an overnight interruption of the continuous IV flucloxacillin for 8 hours during which period the patients also fast. Thereafter, an oral dose of 1g of flucloxacillin was given. Serum flucloxacillin was measured before, and at 1, and 2 hours after the oral dose. In the second test (test B), IV flucloxacillin was continued and the 1g oral dose was given after a fast of at least 1 hour. Measurement of flucloxacillin concentrations was at the same times as in test A. These sample times were chosen because the time of maximal concentration is, on average, at 1 hour after intake. However, the time to maximal concentrations cannot be predicted reliably for individual patients, and it was therefore decided to take samples at 1 and 2 hours as this would allow assessment of the absorption also in case of diminished gastrointestinal motility. Adequate absorption was defined as an increase in flucloxacillin concentration of at least 10 mg/l at either sampling time.

FLUCLOXACILLIN ASSAY

Flucloxacillin serum concentrations were determined using a validated high performance liquid chromatography (HPLC) method with ultraviolet detection (all apparatus from Dionex Corporation, Sunnyvale). In short, 10 microliter of a 1 mg/l of cloxacillin solution (Sigma) and 0.5 ml of acetonitril (Promochem) were added to 0.5 ml of thawed patient serum sample. The samples were then vortexed for 5 seconds and subsequently centrifuged for 5 minutes at 25,000g. Thereafter, 0.8 ml of the supernatant was transferred to a 10-ml polypropylene test tube, and 3.5 ml of chloroform (Merck) was added.

The samples were vortexed for 5 seconds and centrifuged for 3 minutes at 5,500g. Of the aqueous upper layer, 0.1 ml was mixed with 0.1 ml of acetate buffer (0.1 mole/l), and 20 microliter of 68 (39–87) 68 (37–179) this solution was assayed by HPLC. The chromatographic system consisted of an octadecylsilica Hypersil stationary phase (3 mm particle size, length 12.5 cm, id 4.6 mm), and a mixture of 1 mole/l acetate buffer solution (pH 6), water, and acetonitrile (40 + 710 + 250, vol/vol) as mobile phase. Flow rate was 1.0 ml/min, and detection took place at a wavelength of 210 nm. A flucloxacillin reference solution in serum was pretreated in the same manner as for the patient samples. This solution was used to determine the flucloxacillin/cloxacillin signal ratio in patient samples. From this ratio, the serum concentrations of flucloxacillin were calculated. The lower limit of quantification (inaccuracy and imprecision <15%) is 3 mg/l, and the assay shows linearity for flucloxacillin concentrations up to at least 100 mg/l. Accuracy of a quality control sample at 40 mg/l tested 15 times over a 1-month period was 111% and precision, expressed as the coefficient of variation, was 4.0%.

DATA ANALYSIS

The data are summarized as mean with SD and range or as median and range. The maximal concentrations reached in each test variant were compared using an unpaired Student *t*-test. Linear regression analysis was performed regarding the relationship between age, serum creatinine, and pretest concentration and the maximal concentrations.

RESULTS

The study population consisted of 43 patients (18 female, 25 male) treated with IV flucloxacillin with an individualized dose ranging from 6–12g/d. The OATs were performed in groups with similar baseline characteristics (*table 1*). The majority of the patients had treated comorbidities such as hypertension (46%), type 2 diabetes mellitus (21%), or hypercholesterolemia (40%) or combinations thereof and were in addition treated with other drugs including antacids (46%), psychoactive drugs (21%; mainly benzodiazepines), or analgesics or antithrombotics (23%, mainly heparins and occasional antiplatelet agents). There was no difference in age, renal function, gender, diagnoses, or comedication. Test A was performed in 19 patients and test B in 24 patients. The maximally observed increase was highly variable between patients (*figure 1*). The average (SD; range) maximal increase for test A was 21.7 (11.3; 7–50) and 26.1 (12.8; 8–53) mg/l for test B. There was no significant difference in the maximal increase in flucloxacillin concentration between the test variants (p=0.23). Also, there was no relationship between age (r^2=0.06), serum creatinine (r^2=0.01), or pretest flucloxacillin concentration (r^2=0.01) and the observed maximal concentration.

In 4 of the 43 patients (9%), the maximal increase in flucloxacillin concentration did not reach the predefined value of 10 mg/l. This was found in 1 patient using test variant A and 3 patients using test variant B. This difference does, however, not mean that one test variant is more sensitive than the other but reflects the relative small sample size and the inherent variability in absorption. Indeed, if a cut-off value of 12.5 mg/l had been used, both test variants would have identified 16%–17% of the population as poor absorbers. The majority of the concomitant medications used by

patients and gastrointestinal conditions present in the patients who absorbed well and patients who absorbed poorly were alike. Therefore, there were no reasons to a priori suspect impaired flucloxacillin absorption in any of these patients. Specifically, 2 patients who showed poor absorption were treated for preexisting diabetes, but this was also present in another 18 patients who absorbed well. Also, retrospectively, no remarkable clinical condition or drug use that may have impaired flucloxacillin absorption could be identified.

DISCUSSION

Patients with severe methicillin-sensitive *S. aureus* infections are effectively treated with initial continuous IV flucloxacillin for at least 2 weeks, which, if effective is often followed by an additional 2–4 weeks of oral maintenance therapy. There are many advantages to start oral therapy as soon as possible including, but not limited to, ease for the patient and the possibility to treat on an outpatient basis. However, the reliability of an early switch to oral dosing may be complicated by the highly variable oral flucloxacillin absorption, which may jeopardize treatment outcome. Treatment failure due to insufficient absorption can be avoided by performing an OAT, and this is commonly practiced in our institution.

We were used to employ test A, which starts with interruption of the continuous IV flucloxacillin for 8 hours during which period the patients also fast. Thereafter, an oral dose of 1g of flucloxacillin is given. Serum flucloxacillin is measured before, and at 1 and 2 hours after the oral dose. However, this test variant is cumbersome and possibly even less safe as the flucloxacillin levels are below the MIC for several hours due to interruption of the IV therapy. Therefore, we explored if equal results could be obtained with a test variant in which IV dosing is continued while the oral test dose is given. This approach was deemed feasible as it has been shown that flucloxacillin has a wide therapeutic ratio and thus (short term) exposure to higher concentrations is safe and well accepted. In addition, with this approach the practical disadvantages of the earlier test variant such as the need to timely stop and restart the IV pump are avoided. Thus, the new approach is easier executed by the nursing staff and likely reduces mistakes and need for retesting.

We confirm the large interindividual variability in oral flucloxacillin absorption,[3,5] and this was similarly detected with both test variants. We chose to apply a cut-off value of 10 mg/ L, because the MIC of the isolated cultures was <1 mg/l of (free) flucloxacillin. With this criterion, our results indicate that a significant proportion (10%) of the hospitalized patients show insufficient oral absorption. Obviously, the cut-off value can be adapted for individual patients based on MIC of the isolated strain for flucloxacillin, but this is rarely necessary. Also, the findings can assist in determining the dose regimen for oral flucloxacillin that will be prescribed. Although this study did not specifically address intrapatient variability, our experience is that patients who absorb well generally do consistently so in repeat tests, while in patients who are identified as poor absorbers more variable results are obtained during retesting. A potential weakness of our findings is that we did not study test B in a sufficient number of patients with severe renal dysfunction which can affect flucloxacillin disposition. However, based on pharmacokinetic principles and our clinical experience with test variant A, we argue that test B ought to perform adequately in those patients, but this should be verified. Taken together, we provide a simpler and robust, test variant with lesser burden for physicians, nursing and laboratory personnel. In addition, the HPLC-based assay for flucloxacillin is easy to perform and can be implemented in hospital pharmacies at low equipment or staff costs. With the adaptations that we have done, we introduce a simple test that may be considered in applicable cases to guide transition from IV to oral maintenance therapy of flucloxacillin.

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FIGURE 1 **Box and whisker plots for the maximal increase in flucloxacillin at either 1 or 2 hours after an oral dose of 1g using test variants A and B (interruption or continuation of the IV flucloxacillin, respectively). The individual data are indicated by the symbols, the horizontal line across the box shows the median, the boxes indicate the 25th to 75th percentile of the data and the whiskers from the edge of the box are the 5th and 95th percentiles. The dashed line indicates the cut-off value at 10 mg/l.**

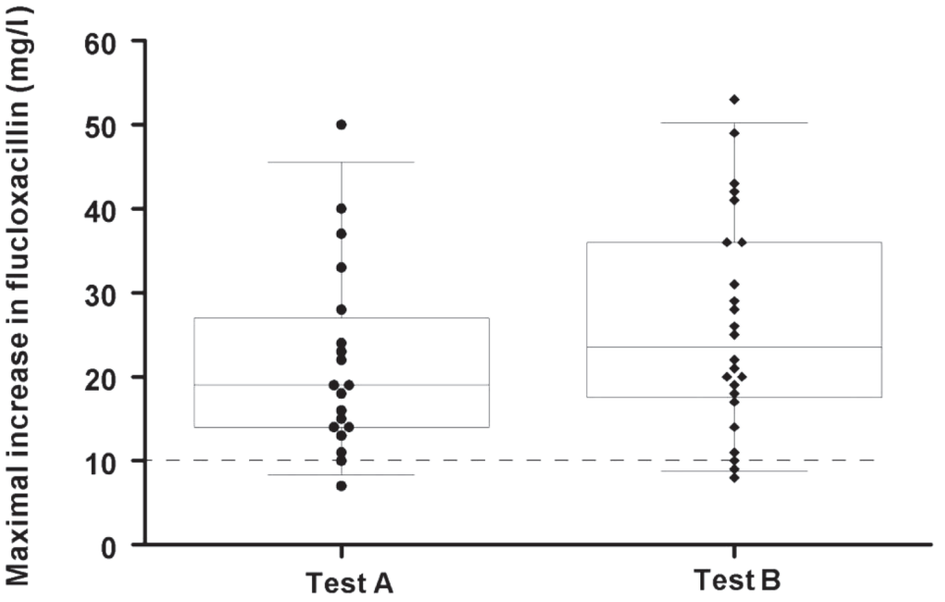

TABLE 1 **Population Characteristics.**

	Test A		Test B	
Number of patients	19		24	
Gender	8 F	11 M	10 F	14 M
Age (yrs)*	63 (18–83)	58 (39–77)	68 (26–85)	64 (20–88)
Creatinine in serum (µmole/l)*	51 (34–89)	70 (39–120)	68 (39–87)	68 (37–179)

**Median (range)*