Single-dose pharmacokinetics of ampicillin and tobramycin administered by hypodermoclysis in young and older healthy volunteers

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1 To test the feasibility of administering antibiotics by subcutaneous infusion to the elderly, we compared the pharmacokinetics of tobramycin (single dose of 80 mg) given by hypodermoclysis (HDC) with the kinetics of the antibiotic injected intravenously (i.v.) in 10 young (< 50 years old) and 10 elderly (> 65 years old) healthy volunteers. Similar studies were performed with ampicillin (single dose of 1 g) in 12 young and 10 older healthy volunteers.

2 Compared with the i.v. route, HDC delayed the time to reach the maximal plasma concentration ($t_{\text{max}}$) of tobramycin in young volunteers: $32 \pm 6$ (s.d.) min vs $88 \pm 46$, $P < 0.005$, and older volunteers: $27 \pm 4$ min vs $89 \pm 15$, $P < 0.005$. Administration of the antibiotics by HDC was well tolerated. The plasma concentration of tobramycin 30 min after the end of infusion ($C_{60}$) was lower ($P < 0.05$) following HDC than after the i.v. route in both young, $2.2 \pm 0.7$ vs $3.5 \pm 0.8$ µg ml$^{-1}$, and elderly subjects, $2.2 \pm 0.8$ vs $3.8 \pm 0.9$, µg ml$^{-1}$.

3 The area under the curve (AUC) of tobramycin given by HDC was slightly smaller than when given i.v., i.e. in young subjects: $740 \pm 225$ (s.d.) vs $893 \pm 223$ µg ml$^{-1}$ min, NS, and in the elderly: $980 \pm 228$ vs $1056 \pm 315$ µg ml$^{-1}$ min, NS.

4 When ampicillin was administered by HDC, the $t_{\text{max}}$ was also delayed in young volunteers: $45 \pm 18$ vs $23 \pm 6$ min, and in the elderly: $49 \pm 18$ vs $27 \pm 4$ min, $P < 0.005$, the AUC was greater by HDC than i.v. in the young volunteers: $4527 \pm 1658$ µg ml$^{-1}$ min vs $3810 \pm 1033$ µg ml$^{-1}$ min and in the elderly: $6795 \pm 2094$ µg ml$^{-1}$ min vs $4217 \pm 1518$ µg ml$^{-1}$ min, and the $C_{60}$ was higher by HDC in the young: $27 \pm 7$ vs $24 \pm 9$ µg ml$^{-1}$, and in the elderly: $32 \pm 9$ vs $23 \pm 11$ µg ml$^{-1}$, $P < 0.05$.

5 In conclusion, HDC delays the entry of the antibiotic into the systemic circulation, but did not affect the amount available. HDC was well tolerated and could become an adequate method for antibiotic administration to the elderly.

Keywords hypodermoclysis antibiotics pharmacokinetics elderly

Introduction

Moderate infections in elderly patients living in chronic care institutions may require the administration of antibiotics through an intravenous (i.v.) route and such treatment may complicate their transfer to hospitals.

Hypodermoclysis (HDC), the subcutaneous infusion of a solution using hyaluronidase to enhance its diffusion, was introduced about 50 years ago [1–9]. It became obsolete with the development of i.v. catheters but is still employed for geriatric and palliative care hydration when the access to veins is complicated [10–20].

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Some drugs have been successfully administered by HDC [10, 15, 17, 20], but HDC is seldom used for drug therapy and has not yet been recommended officially.

Antibiotics given by this route could reduce the number of patients being transferred from chronic care institutions to hospitals. However, the efficacy and toxicity of antibiotic delivered by HDC have not been sufficiently documented. The present studies were designed to assess the usefulness of HDC for the administration of ampicillin, a beta-lactam antibiotic, and tobramycin, an aminoglycoside. Firstly, the local toxicity of the antibiotics administered by HDC was assessed in young healthy volunteers. Secondly, the pharmacokinetics of a single dose of ampicillin and tobramycin were documented in young and elderly healthy volunteers administered by HDC in comparison to the i.v. route.

Methods

The protocol was approved by the Centre de Recherche Hôpital-Dieu de Montréal’s ethics committee. All subjects gave written informed consent after full explanation of the experimental procedure.

Toxicity study

Local toxicity was examined in 16 healthy volunteers following the HDC administration of either ampicillin or tobramycin. All subjects were younger than 40 years of age, and had no history of hypersensitivity to either antibiotic. All subjects were healthy, as judged by a normal physical examination and normal routine blood tests including serum creatinine. Preliminary tests showed no hypersensitivity to hyaluronidase before the beginning of infusion. Each volunteer was then infused 50 ml of NaCl 0.9% containing 75 units of hyaluronidase for 30 min in both thighs. The solution infused subcutaneously in the left thigh with a butterfly catheter contained 0.5 g of ampicillin or 40 mg of tobramycin. Standard doses of 1 g of ampicillin and 80 mg of tobramycin were not used in this pilot toxicity study. In addition, 75 units of hyaluronidase were injected subcutaneously at the catheter insertion site on both thighs. Those two separate 75-unit doses of hyaluronidase are used regularly for hypodermoclysis in an affiliated chronic care hospital. Frequent inspections were undertaken for local signs of pain, warmth, swelling and redness of the skin where the catheter was introduced. All subjects were evaluated for 3 h and during this time, they used a visual analogue scale to describe the pain they felt.

Pharmacokinetic study

A group of 17 volunteers aged between 17 and 50 years and a second group of 10 volunteers aged over 60 years participated in the pharmacokinetic study. All subjects were healthy, as judged by a normal physical examination and normal routine blood tests including serum creatinine. None was known to be hypersensitive to the antibiotics and a pretest ruled out hypersensitivity to hyaluronidase. A subgroup of young (n = 12) and elderly volunteers (n = 10) participated in the ampicillin arm of the pharmacokinetic study, while another subgroup of young (n = 10) and the same elderly subjects (n = 10) participated in the tobramycin arm. Five young healthy volunteers participated in both arms of this study. Within each antibiotic subgroup, all subjects, whether young or old, received a dose of the antibiotic through the i.v. route and the same dose by HDC, after a 1 week interval. The order of administration (i.v. vs HDC) was not randomized. With both routes, the dose of ampicillin used was 1 g for all individuals, and the dose of tobramycin was 80 mg. The antibiotics were diluted in 50 ml of NaCl 0.9% and infused i.v. over a 30 min period, and by HDC over a 20 min period. For HDC, 75 units of hyaluronidase were mixed with the antibiotic solution and another 75 units were injected subcutaneously at the catheter site. Local toxicity was monitored in all cases. Blood samples for the determination of serum antibiotic concentrations were drawn at 0, 10, 15, 20, 25, 30, 35, 40, 45, 60, 90, 120, 150, 210, 270, 330 and 390 min for the i.v. route, and at 0, 10, 20, 22.5, 25, 30, 45, 60, 90, 120, 150, 210, 270, 330 and 390 min for HDC. Time 0 corresponds to the beginning of infusion. Time 60 min (30 min following the end of infusion) was specifically taken into account since it corresponds to a clinically relevant parameter approximating the time of peak concentration for the adjustment of aminoglycoside dosage. Blood samples were immediately centrifuged at 4°C and plasma samples were frozen at −20°C in the case of tobramycin, until analysis, but in the case of ampicillin, plasma samples were assayed on the same day without prior freezing.

Analytical methods

Plasma ampicillin was measured by biological assay: a standard curve was drawn for the inhibition of Sarcina lutea (ATCC 9341) growth. Blood samples from patients given ampicillin were then tested for inhibition of this bacteria [21]. Plasma tobramycin was measured by immunoenzymatic assay (EMIT®, Syva Corporation, Palo Alto, CA, USA) [22].

Pharmacokinetic analysis

Maximum serum concentration of the antibiotics (Cmax) was established by visual inspection of serum concentration vs time curve. The time required to reach this maximum serum concentration was defined as tmax. The elimination rate constant (λz) was calculated by linear regression of the terminal phase of plasma concentrations until the last measurable concentration (Cmin). The area under the concentration vs time curve (AUC) was calculated by the linear trapezoidal method up to

the last measurable serum concentration to which was added the value of the $C_{\text{max}}/\lambda_\alpha$ ratio. Terminal half-life ($t_{1/2}$) was calculated as 0.693 divided by $\lambda_\alpha$.

**Statistical analysis**

The effects of age (elderly vs young subjects) and route of administration (HDC vs i.v.) were statistically assessed by analysis of variance (ANOVA), the antibiotic subgroups being considered separately. Anthropometric data and creatinine clearance were evaluated by Student’s $t$-test. Analysis of co-variance was used to assess the contribution of body surface area (BSA) and creatinine clearance to pharmacokinetic differences related to age or route of administration. BSA was calculated as: $0.007184 \times [\text{body weight}^{0.425} \times [\text{height}^{0.725}]]$, where body weight is in kg and height is in cm.

**Results**

**Toxicity study**

The subcutaneous infusion of both antibiotics was generally well tolerated. None of the subjects reported any pain on the visual analogue scale with the use of tobramycin, and only one of the eight subjects given ampicillin had a light pain which lasted for 25 min after infusion. Warmth and erythema were found locally with both ampicillin (three subjects) and tobramycin (one subject) as well as with the vehicle alone (two subjects).

**Pharmacokinetic study**

As shown in Table 1, the young volunteers were taller, had a similar body weight and higher BSA than the elderly subjects and, as expected, higher creatinine clearance. Antibiotic infusion during the pharmacokinetic study was well tolerated (no pain) in all subjects. In the tobramycin arm, technical problems occurred during infusion of the antibiotic in one young subject, and these data were excluded from the analysis.

Antibiotic plasma concentrations administered by HDC as a function of time rose much more slowly than with the i.v. infusion (Figures 1 to 4). As a consequence, the $C_{\text{max}}$ of antibiotics given by HDC was lower and

![Graph showing plasma ampicillin concentrations](image1.png)

**Figure 1** Plasma ampicillin concentrations (mean $\pm$ s.d.) vs time in young volunteers after single-dose administration of 1 g ampicillin by HDC (---) and i.v. (—). Time 0 corresponds to the beginning of infusion.

![Graph showing plasma ampicillin concentrations](image2.png)

**Figure 2** Plasma ampicillin concentrations (mean $\pm$ s.d.) vs time in older volunteers after single-dose administration of 1 g ampicillin by HDC (---) and i.v. (—).

<table>
<thead>
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<th>Table 1 Anthropic data (mean $\pm$ s.d.)</th>
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<td><strong>Ampicillin</strong></td>
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<td>Age (years)</td>
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<td>Height (m)</td>
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<td>Weight (kg)</td>
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<td>BSA (m²)</td>
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<td>$CL_{\text{cr}}$ (ml s⁻¹)</td>
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BSA: body surface area; $CL_{\text{cr}}$: creatinine clearance.

* $P<0.05$ vs young; † $P=0.05$ vs young.

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administered i.v. This observation was independent of the age. In addition, in the elderly, the tobramycin elimination rate constant was smaller than in young volunteers in both route of administration (Table 3). Consequently, the estimated half-life of tobramycin was longer when the antibiotic was administered by HDC than by i.v. On the other hand, the elimination rate constant and the terminal half-life in older subjects was smaller than in young volunteers. Systemic clearance of tobramycin was smaller in older subjects than in young volunteers in both route of administration. Relative bioavailability, \( \frac{AUC_{HDC}}{AUC_{i.v.}} \), or \( F \), was 0.92±0.36 and 0.96±0.16 in young and older subjects respectively (NS). Tobramycin volume of distribution was larger in older subjects than in the young volunteers when the antibiotic was administered i.v.; this difference was not so apparent (\( P > 0.005 \)) in young volunteers (Table 3).

Discussion

The kinetics of ampicillin and of tobramycin infused intravenously to healthy young or elderly volunteers are in perfect agreement with the data published in the literature [23]. As expected, because of a reduced renal function in the elderly, the apparent clearance of ampicillin and of tobramycin were lower than the values estimated in the young volunteers.

The results of the present study show that antibiotics administered by HDC enter the systemic circulation more slowly than when administered by i.v. infusion, as reflected by a lower \( C_{\text{max}} \) and a longer \( t_{\text{max}} \) in young and elderly subjects. It is to be expected that the administration of hydrosoluble and large molecules by HDC will reduce the rate of absorption, since to be absorbed the drugs must cross cell membranes. It is interesting to note that age did not influence the rate of absorption of a drug administered by HDC. Administration of ampicillin or tobramycin by HDC does not appear to affect the amount reaching the systemic circulation, since the ratio of HDC over i.v. AUC is almost identical to the ratio of clearance_{HDC} over clearance_{i.v.}.

In both young and elderly volunteers, the AUC of ampicillin administered by HDC was greater than that estimated after the administration of ampicillin i.v. Ampicillin plasma concentrations were assayed by bioassay, and ageing bacteria may jeopardize the stability of the method. However, the assay was very reproducible over a 21-day period. The increase in ampicillin AUC following the HDC administration does not appear to be dependent of the route since the administration of tobramycin by HDC did not yield an AUC greater than that estimated when tobramycin was injected i.v. An increase in AUC may be secondary to an increase in amount absorbed or a decrease in the rate of elimination. Whenever intravenous administration yields a 100% bioavailability, the administration by another route could not increase the bioavailability. Therefore, we must conclude that HDC administration of ampicillin decreases its clearance. Ampicillin is
can decrease urinary pH and facilitate ampicillin elimination essentially by tubular secretion in the kidneys but may be reabsorbed in the distal tubule of the kidney [24]. Active transport is easily inhibited by other substrates employing the same route of elimination [24]. It is not known whether hyaluronidase and/or its metabolites can inhibit ampicillin tubular secretion or can decrease urinary pH and facilitate ampicillin reabsorption. Indeed, further studies will be required to ascertain that hyaluronidase does not modify the kinetics of other xenobiotics.

By comparison with the i.v. route of administration, the terminal half-life of ampicillin and tobramycin was prolonged when administered by HDC to young or elderly volunteers. The increase in terminal half-life may be explained by several mechanisms. Concerning ampicillin in young volunteers, the half-life increased by 45%, but may be reabsorbed in the distal tubule of the kidney.

![Graph or Table](image-url)
in part due to a decrease of \( \approx 10\% \) in clearance and an increase in its volume of distribution by \( \approx 27\% \). In the elderly, the 25\% increment in half-life appears to be the net result between a decrease in both its clearance by \( \approx 40\% \) and its volume of distribution by \( \approx 20\% \). Concerning tobramycin, in both young and elderly, the increase in terminal half-life could be accounted by the increment in volume of distribution observed when administered by HDC. Alternatively, the prolongation of the apparent terminal half-life could be explained by flip-flop kinetics [25] due to slow and prolonged absorption, even if the terminal phase was assumed to start at around 150 min. Following the administration by HDC, the decay of the logarithm of plasma concentrations of ampicillin or tobramycin during the terminal phase in young or elderly volunteers depicts a straight line, indicating that the apparent constant rate of disposition did not change during the period of 150 to 390 min. These results suggest that whenever the increase in apparent half-life of ampicillin or tobramycin is due to flip-flop kinetics, the absorption pattern following HDC is peculiar, i.e. the absorption of both antibiotics is initially rapid, producing a quick raise in plasma concentrations, but followed by a slow and persistent absorption of longer than 6 h. Further studies are required to explain the increase in apparent half-life when a drug is administered by HDC, before it can be recommended to increase the intervals of administration.

The pharmacokinetic parameters derived presented a rather high variability, i.e. usually higher than 20\% (Table 4). The coefficient of variation was slightly lower in the elderly than in young volunteers. In addition, in the elderly the coefficient of variation of a kinetic parameter was not increased when the antibiotic was administered by HDC, except for the \( C_{\text{max}} \) of ampicillin. Whether this is also the case in the frail elderly who might have increased absorption variability due to skin changes, needs to be tested in future study. In young subjects, the coefficient of variation usually increased when the antibiotic was given by HDC.

Sixty minutes after the administration of ampicillin by HDC, its plasma concentration \( (\text{C}_{\text{amp}}) \) was about 30 \( \mu \text{g} \text{ml}^{-1} \). Although this value was lower than the \( \text{C}_{\text{amp}} \) attained following the intravenous administration of ampicillin, it is included in the therapeutic range, indicating that infections normally treated with intravenous ampicillin might be treated by HDC. On the other hand, the \( \text{C}_{\text{amp}} \) of tobramycin administered by HDC was 50\% lower than that observed when administered intravenously, and relatively high plasma \( \text{C}_{\text{amp}} \) are needed for effective eradication of some bacteria [26]. Since the clinical efficacy is closely associated with peak plasma concentrations, the efficacy of tobramycin could be jeopardized because its \( C_{\text{max}} \) and \( C_{\text{ss}} \).

In conclusion, this study demonstrates that by comparison with the i.v. route, the administration of ampicillin and tobramycin by HDC modify slightly the kinetic parameters of both drugs. The small changes in absorption, distribution and elimination are associated with the route of administration but not with the age of the recipient. This study shows the potential usefulness of HDC for the administration of antibiotics or perhaps other drugs. Further studies are warranted to assess the safety of hyaluronidase, and to define precisely with optimal dosage regimen to administer ampicillin or tobramycin.

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References


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