The pharmacokinetics of ketobemidone in critically ill patients

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Aims To study the pharmacokinetics of orally and intravenously administered ketobemidone in critically ill patients.

Methods Seventeen patients were studied during their stay in the intensive care unit at Huddinge University Hospital. Nine patients received a single intravenous dose of ketobemidone (0.04 mg kg^{-1}) and eight patients received a single oral dose of 5 mg. Plasma concentrations of ketobemidone were measured using liquid chromatography-mass spectrometry. The pharmacokinetic analysis was performed using WinNonlinTM software.

Results There was a wide variation in the different pharmacokinetic parameters among patients. Mean clearance in patients treated intravenously was 74.5 (95% CI 43.2, 128.3) and mean V_d was 2.4 l kg^{-1} (95% CI 2.0, 2.8). $t_{1/2,z}$ also varied widely with a mean value of 4.41 h (95% CI 2.7, 7.0). The corresponding values for MRT were 5.4 and 3.3, 8.8. Mean oral clearance (CL/F) was 102 l h^{-1} (95% CI 82.7, 125.8), mean V_z/F was 11.2 l kg^{-1} (95% CI 9.7, 13.1) and mean $t_{1/2,z}$ was 6.0 (95% CI 4.9, 7.3) in orally treated patients. C_{max} showed a mean of 38 nmol l^{-1} (95% CI of 31, 47). A significant correlation was observed between the glomerular filtration rate (GFR) and the half-life of ketobemidone ($r = -0.72$, $P < 0.05$). $t_{1/2,z}$ was generally longer and the variation larger in critically ill patients compared with healthy individuals. However, there was no correlation between the elimination of ketobemidone in critically ill patients and plasma C-reactive protein, white blood count or plasma albumin concentrations.

Conclusions The disposition of ketobemidone is highly variable in critically ill patients. In order to ensure sufficient analgesia and avoid toxicity, therapeutic monitoring should be employed when using ketobemidone in this group of patients.

Keywords: critically ill patients, ketobemidone, pharmacokinetics

Introduction

Ketobemidone is a potent narcotic analgesic that has long been used in the management of severe pain. Although the drug is frequently used in intensive care units in Scandinavia, data on its pharmacokinetics in this patient category are lacking. Patients requiring intensive care often display marked abnormalities that might have a significant impact on the disposition of drugs [1]. Changes in liver and renal function, severe inflammatory processes, expanded extracellular volume are common aberrations in the intensive care setting. In the present

work, we have investigated the pharmacokinetics of orally and intravenously administered ketobemidone in critically ill patients.

Methods

Patients

Seventeen patients with different medical and surgical diagnoses were enrolled during their stay in the intensive care unit (ICU) at Huddinge University Hospital. Mean age was 64 years (range 30–86) and mean weight was 81 kg (range 65–104). Most of the patients had sepsis and five had renal failure. Many had laboratory signs of hepatic dysfunction but none developed liver failure. Glomerular filtration rate (GFR) was calculated using the formula of Cockcroft & Gault: $\text{GFR}_{\text{ml min}^{-1}} = 1.2 \cdot (140 - \text{age}_{\text{yr}}) \cdot \text{weight}_{\text{kg}} / \text{p-creatinine}_{\mu\text{mol l}^{-1}}$.

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When clinically indicated, patients received a single intravenous (0.04 mg kg^{-1} body weight) or oral dose (5 mg) of ketobemidone, given via a gastric tube. Eight patients were treated orally and nine intravenously. Blood samples for analysis of ketobemidone were drawn immediately before and 10 min, 20 min, 30 min, 40 min, 1, 2, 3, 4, 5, 8, 12 and 24 h after dosing.

Informed consent was obtained from the patient or a close relative when direct communication with the patient was not possible. The study protocol was approved by the Ethics Committee at Huddinge University Hospital.

Analysis of ketobemidone

Ketobemidone was determined in plasma samples using solid-phase extraction and liquid chromatography–mass spectrometry [2]. Coefficients of variation (CV), measured at 5.0 nmol l^{-1} and 38.9 nmol l^{-1} ranged from 2.8 to 4.9%. The limit of quantification was 3 nmol l^{-1} . In one patient, it was not possible to obtain reliable concentrations due to chromatographic interference and the patient was not included in the subsequent pharmacokinetic analysis. In another patient, the concentrations of ketobemidone were below the limit of quantification in the majority of samples, rendering pharmacokinetic analysis impossible.

Pharmacokinetic analysis

Intravenous administration

Plasma concentration data were fitted to a two-compartment model with i.v. bolus input and first order elimination using WinNonlin™ software [3]. The following pharmacokinetic parameters were estimated: area under the concentration curve (AUC), terminal half-life ($t_{1/2,z}$), volume of distribution (V_d), clearance (CL), mean

residence time (MRT) and volume of distribution at steady state (V_{ss}).

Oral administration

Oral clearance (CL/F), AUC, peak plasma concentration ($C_{\max}$), time to reach $C_{\max}$ ($t_{\max}$), $t_{1/2,z}$ and apparent volume of distribution (V_z/F) were calculated by noncompartmental analysis (NCA) using the same software as above.

Statistical analysis

Linear regression was used to study the correlation between pharmacokinetic parameters and covariates. The tests were considered statistically significant for P value < 0.05 .

Results

The pharmacokinetic parameters for ketobemidone after intravenous and oral dosing are shown in Table 1.

Intravenous administration

There was wide variation in each of the parameters among patients. CL values ranged from 21.9 to 356.6 l h^{-1} and the V_d from 1.7 to 3.4 l kg^{-1} . $t_{1/2,z}$ varied between 1.3 and 10.4 h . The corresponding range for MRT was 1.5 – 14.2 h .

Oral administration

CL/F varied between 71.3 and 159.8 l h^{-1} , V_z/F between 8.56 and 16.67 l kg^{-1} and $t_{1/2,z}$ between 4.6 and 9.5 h . $C_{\max}$ ranged from 27 to 63 nmol l^{-1} . Time to reach peak concentration did not vary substantially although one patient displayed a delayed absorption with $C_{\max}$ reached 2 h after drug intake.

Table 1 The pharmacokinetic parameters of intravenously (0.04 mg kg^{-1} body weight) and orally (5 mg) administered ketobemidone to critically ill patients.

<i>I.v. administration</i>	AUC_{last} (nmol l h^{-1})	Clearance (l h^{-1})	$t_{1/2,z}$ (h)	MRT (h)	V_d (l kg^{-1})	V_{ss} (l kg^{-1})
Mean	176.9	74.5	4.4	5.4	2.4	4.9
95% CI	100.9, 310.1	43.2, 128.3	2.7, 7.0	3.3, 8.8	2.0, 2.8	4.2, 5.7
<i>Oral administration</i>	AUC_{last} (nmol l h^{-1})	CL/F (l h^{-1})	$t_{1/2,z}$ (h)	$C_{\max}$ (nmol l^{-1})	$t_{\max}$ (min)	V_z/F (l kg^{-1})
Mean	156.4	102.0	6.0	38	48	11.2
95% CI	131.7, 185.8	82.7, 125.8	4.9, 7.3	31, 47	34, 67	9.7, 13.1

AUC_{last} , area under the plasma concentration curve between time 0 and time of last measured concentration above the lower limit of quantification; $t_{1/2,z}$, terminal half-life; MRT, mean residence time; V_d , volume of distribution; V_{ss} , volume of distribution at steady state; CL/F, oral clearance; $C_{\max}$, peak plasma concentration; $t_{\max}$, time to reach $C_{\max}$; V_z/F , apparent volume of distribution.

Figure 1 a) The relationship between the glomerular filtration rate (GFR) and the elimination half-life of ketobemidone; b) the elimination half-life of ketobemidone in critically ill patients and healthy volunteers. Data on healthy volunteers comes from reference 3.

A significant correlation was observed between GFR and $t_{1/2,z}$ of ketobemidone (Figure 1a). However, there was no correlation between $t_{1/2,z}$ and the concentrations of C-reactive protein, and plasma albumin, or white blood count (not shown).

Discussion

The pharmacokinetics of ketobemidone have mainly been studied in healthy volunteers [4] and surgical

patients [5–7]. Studies in the critically ill have not been performed, although the drug has been used in Scandinavian intensive care units for many years. The present data show that the disposition of ketobemidone varies widely among critically ill patients. Further, these patients appear to display lower values for clearance/oral clearance and longer $t_{1/2}$ and MRT compared with those reported in healthy volunteers [4] (Figure 1b). The reason for this is most probably multifactorial.

The elimination of ketobemidone is clearly affected by the renal function as indicated by the correlation between GFR and $t_{1/2}$ (Figure 1a). Patients with renal failure displayed exceptionally low values for clearance and also the longest observed MRT and $t_{1/2}$. This is consistent with the finding that a substantial fraction (26–67%) of a dose of ketobemidone is excreted in the urine as free and conjugated drug [4, 8]. Furthermore, haemodiafiltration seems to increase the elimination of ketobemidone. Hence, oral clearance was not severely affected by renal failure in a patient undergoing haemodiafiltration. Another patient whose plasma creatinine was normalized via haemodiafiltration showed plasma concentrations of ketobemidone that were consistently near or below the detection limit of the assay. Although the effect of haemodiafiltration on the disposition of ketobemidone should be studied before any definite conclusion can be drawn, our findings suggest that ketobemidone might be better avoided in the latter group of patients unless plasma concentrations are monitored and the dose is adjusted accordingly.

Ketobemidone has been shown to undergo hepatic metabolism with glucuronidation and N-demethylation as major pathways [8]. Therefore, it is conceivable that a reduced hepatic metabolic capacity would lead to impaired metabolism of the drug. Prolonged INR in the absence of warfarin treatment is usually considered a sign of decreased metabolic capacity, and in our study two patients with INR above the normal range displayed signs of impaired elimination. One of them had a $t_{1/2}$ of 9.5 h, the second highest value observed in the study, and more than twice as high as the mean value reported for healthy volunteers [4]. However, the other patient had been tetraplegic for several years and his plasma creatinine concentration of $84 \mu\text{mol l}^{-1}$, albeit within the 'reference interval' might indicate some reduction in GFR. Indeed, some days after the study, the patient improved clinically and his plasma creatinine fell to $50 \mu\text{mol l}^{-1}$ and remained constant thereafter. Thus, this patient had both reduced renal function and reduced hepatic metabolic capacity during the study period. This probably explains why he showed one of the lowest clearance values for ketobemidone in this group of patients.

In a liver transplantation patient with evidence of

hepatocellular injury (high ALT) but with normal INR, a relatively low value for ketobemidone clearance value was observed. None of our patients had liver failure or known underlying chronic liver disease. Patients with such conditions can be expected to show more severe reductions in the clearance of ketobemidone.

A surprisingly high clearance (356 l h^{-1}) along with rapid elimination ($t_{1/2}$ of 1.5 h) was observed in a patient with pneumonia. This patient was concurrently treated with rifampicin, a powerful inducer of CYP3A4 in the liver. We have recently shown that the pharmacokinetics of ketobemidone are not affected by the CYP2D6 or CYP2C19 phenotype [4]. Our findings in this particular patient imply that the oxidative metabolism of ketobemidone might be mediated by CYP3A4. To our knowledge, this has not been shown previously. Patients who are being treated with enzyme inducers should be monitored to avoid the potential risk of developing subtherapeutic concentrations of ketobemidone.

Although many of the patients investigated in the present work did not have any evidence of severe kidney or liver damage, the pharmacokinetics of ketobemidone in this group seem to be affected by their severe illness. Indeed, the terminal half-life of ketobemidone in these patients appeared to be significantly longer and displayed a wider variation compared with that reported in healthy volunteers [4] (Figure 1b). However, the elimination of ketobemidone did not correlate with the inflammatory response, as indicated by plasma CRP concentration and white blood count. Further, there was no correlation between plasma albumin concentrations, a biochemical measure of the severity of disease, and the elimination of the drug. However, the pathological processes underlying critical illness are complex and the biochemical parameters routinely used might fail to disclose factors that potentially affect the capacity of the body to metabolize and eliminate drugs.

The finding that t_{max} for ketobemidone might be as long as 2 h (Table 1) suggests that oral administration may not be adequate in critically ill patients needing analgesia.

The analgesic effect of ketobemidone is related to its plasma concentrations [9], and a mean minimum effective concentration of $100 \pm 44 \text{ nmol l}^{-1}$ has been suggested [10]. Very little is known about the concentrations associated with toxic effects. In our own experience, continuous ketobemidone infusion, which is common clinical practice, leads to plasma concentrations as high as 500–1000 nmol l^{-1} in intensive care patients, which may explain symptoms such as drowsiness and the difficulty in weaning patients off assisted ventilation. Furthermore, signs of opiate overdosage might be difficult to assess in

severely ill patients on polypharmacy. Therefore, it is prudent to monitor plasma concentrations of ketobemidone in these patients.

To summarize, our study shows that the disposition of ketobemidone is highly variable in critically ill patients. Renal insufficiency, liver dysfunction, comedication with enzyme inducers and critical illness *per se* are factors that affect the pharmacokinetics of ketobemidone. Because of this variability, it is inadvisable to use standard doses of ketobemidone in the critically ill. This policy might lead to sub-analgesic plasma concentrations in some patients and toxic concentrations in others. The use of ketobemidone in the ICU should be monitored by plasma concentration determination.

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