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Baclofen self-poisoning: is renal replacement therapy efficient in patient with normal kidney function?

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Abstract:

Aims: We aimed at assessing the effectiveness of renal replacement therapy in patients severely self-poisoned with baclofen and with normal kidney function.

Methods: A population pharmacokinetic model was built using analytical data extracted from 26 baclofen poisoning cases reported to a French Poison Centre: 8 patients underwent renal replacement therapy (RRT), 18 did not. In the RRT group, 2 patients suffered from kidney failure. Mechanical ventilation was required for 20 patients with normal kidney function; 15 were not treated by RRT and 5 were. Pharmacokinetic profiles of baclofen were measured in 28 patients and further modelled by a non-parametric approach (PMetrics®). The total data set was divided into a building data set (26 patients, 57 observations) and a validation set (2 external patients, 6 observations). Then, the estimated elimination half-life of baclofen and the duration of intubation were compared in patients with or without RRT using Wilcoxon–Mann–Whitney test.

Results: A model using three parameters plus a lag time and bioavailability was necessary to determine the pharmacokinetics of baclofen. Estimated elimination half-life in the 'RRT' group and the 'no RRT' group were respectively 3.1 [2.2-4.8] hours (n = 6 patients) and 3.4 [1.4-5.5] hours (n = 19 patients, p = 0.53). The median duration of intubation was not significantly different between groups (72 [48-72] hours and 72 [24-96] hours, respectively; p = 0.38).

Conclusion: Renal replacement therapy did not appear to significantly increase baclofen clearance in patients without kidney failure.

Keywords: baclofen, haemodialysis, intoxication, extra-renal purification

1. Introduction

Baclofen was originally used for treating central spasticity. Olivier Ameisen, a cardiologist, described in a best-seller book how he cured his alcohol addiction with daily high doses of baclofen [1]. Baclofen, which is a derivative of γ-aminobutyric acid, is a selective agonist of the receptor GABA(B). This pharmacological profile explains the putative addictolytic and anti-craving properties, through its action on the reward circuit [2].

The number of cases of self-intoxication with baclofen in France has increased since the drug began to be prescribed to treat alcohol addiction. When prescribed in high doses, baclofen can cause severe poisoning. Neurological disorders (coma, seizures, respiratory depression) and cardiovascular complications (lengthening of QT interval, bradycardia, and high blood pressure) have been described. To date, only a few cases of death caused by baclofen have been reported in the literature [3–5].

Severe baclofen poisoning requires intensive supportive care. Treatment is symptomatic, with supportive care and mechanical ventilation if required. In patients with kidney failure, the half-life is enhanced significantly [6] and therefore potentially associated with a prolongation of the toxic effects of the molecule. While the place of renal replacement therapy (RRT) seems established to treat patients with renal failure, it remains controversial for poisoning in patients without kidney dysfunction [7]. This study was based on retrospective biological data collected from patients hospitalised for suicidal ingestion of baclofen and aimed to define the effectiveness of RRT in the treatment of severely poisoned patients with normal kidney function.

2. Materials and methods

We retrospectively collected baclofen poisoning cases reported to the Western Poison Control Centre (PCC) (Angers University Hospital, Angers, France), retrospectively. The Angers University Hospital ethics committee approved this study and waived the need for patient consent (approval number: 2015-89).

In the West French region (corresponding to 12 million inhabitants), we identified all cases of oral intentional baclofen poisoning in patients with normal kidney function treated with RRT reported to the western PCC up to the 31st of December 2015 from spontaneous reports. The cases between January 2012 and December 2015 were reviewed.

Data used in this study came from phone declarations from all emergency departments and intensive care units of Western France to Western PCC. All cases with a known dose of baclofen ingested as well as at least one plasma measurement of baclofen collected were included.

Clinical and paraclinical severity was assessed according to the poisoning severity score. [8].

2.1 Analytical methods

The assays of baclofen were mainly performed by liquid chromatography coupled to tandem mass spectrometry after protein precipitation. This assay method is validated in plasma according to European Medicines Agency (EMA) standards with a linear response for concentrations ranged between 10 and 2000 µg/L (r2> 0.999) and precisions and accuracies below 11.5% [9]. Some laboratories used other methods for analysis. After liquid-liquid extraction by ion pair in alkaline condition, the analysis was performed using a validated LC-DAD method. The internal standard was amoxapin and the detection was performed at 220 nm. The calibration ranged from 0.1 to 4 mg/L [10].

2.2 Pharmacokinetic modelling

All the pharmacokinetics profiles obtained from the 26 overdosed patients were analysed using the non-parametric adaptive grip approach implemented in a R-package (Pmetrics® version 1.5.0) [11]. The total data set was divided into development dataset (26 patients, 57 observations) and an independent validation dataset (2 external patients, 6 observations). Observations meant plasma concentration values of baclofen. Several structural models were assessed during the development process with and without absorption lag time (Tlag) and/or bioavailability (F). The analysis was based on a covariate-free mono-compartment open model: absorption of baclofen was modelled by the first process as described in Figure 1.

The model was parameterised in terms of F, absorption rate constant (Ka), elimination rate (Ke) and apparent central volume of distribution (Vd/F). A linear error model was used to describe the analytical variability.

The performance of the model was appreciated by studying its ability to estimate the individual plasma concentration values of baclofen: the mean bias between the individual plasma concentrations calculated using the individual post hoc parameters and those observed was calculated. Goodness-of-fit plots were also generated including observed versus predicted values at individual levels and weighted residuals *versus* predictions.

The baclofen elimination rate constant was then compared between patients with normal renal function (that is a serum creatinine level below 120 µmol/L or there is no mention of kidney failure in the patient's hospitalisation record) that did or did not undergo renal replacement therapy. Elimination half-life is equal to ln(2)/Ke. Glomerular filtration rates (GFR) were estimated using the MDRD formula. The duration of intubation was also reported to determine the clinical effectiveness of haemodialysis between these two groups.

2.3 Statistical analysis

Between-group comparisons were performed using Wilcoxon–Mann–Whitney test with continuity correction. A Pearson correlation test is used to determine whether the elimination half-life depends on the creatinine blood level value in the study population. A value of $p < 0.05$ was considered statistically significant.

3. Results

In our study, pharmacokinetic profiles were analysed using data from 26 included patients (average number of observations per patient = 2.2 +/-1.7). A structural single-compartment model using three parameters plus a lag time (0 to 4 hours) and bioavailability (0.5 to 0.9) to describe the absorption phase was necessary to determine the pharmacokinetics of baclofen in this population. The model was made of a first-order elimination and an absorption phases described by a gamma distribution, together with a combined analytical error model of $(SD^2 + lambda^2)0.5$ with SD, the standard deviation, modelled by a polynomial equation with up to four terms: C0 + C1*[obs]+ C2*[obs]² + C3*[obs]3 where C0 = 0.01, C1 = 0.1, C2 = 0 and C3 = 0. The run converged after 304 cycles and a weighting factor lambda = 0.02 (i.e. 2 times the C0) was retained with the final model as it improved the precision of concentration and AUC estimates. Figure 2 illustrates the goodness-of-fit of the model.

The relative median bias between the reference and model estimated concentrations was -1.89% (25% quantile: -30.7%, 75% quantile: 17.0%). The scatter plot of observed and individual predicted concentrations showed no major bias (figure 3), and 95% of weighted residuals were within an acceptable range (-2 to 2).

Since this model aimed to estimate drug elimination rate but not to perform PKPOP studies, only two patients that were not used for model-building, served as external validation. The goodness of fit was acceptable (R2 = 0.901) and no major bias was observed (25% quantile: -24.2%, 50% quantile: -0.4%, 75% quantile: 2.60%). Among the 26 patients, 8 underwent RRT during their stay in ICU (4 male and 4

female) including 2 patients suffering from impaired renal function while 18 were not treated by RRT (11 males and 7 females). The population pharmacokinetics parameters are given in Table 1.

In the 24 patients whose renal function was considered normal, the median age of the patients is 39 [30-41] years for the RRT population and 41.5 [33-49] years for the non-RRT population. Two patients were low severity (PSS = 1), 21 were high severity (PSS = 3) and 1 patient died (PSS = 4). Mechanical ventilation was required for 20 patients. Among them, 15 were not treated by RRT and 5 were treated by RRT. Drug or alcohol co-ingestion was reported in 91% of cases. The estimated dose of baclofen ingested (mg), initial baclofen levels in plasma, elimination half-life and the duration of intubation are compared in the Table 2. There were no significant differences in elimination half-lives and duration of intubation between RRT and non-RRT patients. Creatinine blood levels were collected from 18 of the 24 patients who were compared. No correlation was found between creatinine blood levels and elimination half-lives (p = 0.9544).

4. Discussion

Recently, baclofen has provided the hope of being an effective cure of addiction to alcohol, in a context where conventional treatments had modest results at best. However, ingestion of large amounts of baclofen in an attempt to self-arm has been shown to be high-risk. Several reports already insisted on the frequency and severity of baclofen-induced encephalopathy with delirium, seizures, burst suppression on the EEG, leading to mechanical ventilation, aspiration pneumonitis and eventually death [12–16]. Rate of intubation and mechanical ventilation has been reported up to 40 % in a study [17], which is a strong marker of the frequent severity of intoxication. The objective of this work was to determine if RRT is effective in the management of patients self-poisoned with baclofen who had a preserved renal function.

In toxicology, the introduction of RRT in the treatment of acute intoxication presents the advantage of increasing the elimination of toxic substances and shortening the duration of symptoms or severity of the poisoning. Pharmacological and physicochemical properties of baclofen make it a dialysable molecule: hydrosolubility, small molecular weight (213.7 g/mol) and excretion primarily unchanged by glomerular filtration. Multiple case reports of reducing elimination half-life time with renal replacement therapy (RRT) have been published, permitting a clinical improvement [18,19].

Regarding patients with normal renal function, baclofen overdose reported elimination half-lives were up to 15.7 or 34.5 hours for a suspected ingestion of 420 and 450 mg [20,21]. Use of RRT was relatively frequent, notably in patients with normal renal function. It reflects the debate on its

usefulness in baclofen poisoning [7]. Some case reports tried to evaluate the interest of RRT in patients with preserved renal function, with a decrease of elimination half-life, were unable to find superiority of the technique or a clinical benefit [22,23].

Charifou et al. described 8 baclofen-poisoned patients, all managed in the intensive care unit with favourable outcomes. Of these, four patients, including three with normal renal function, were treated with continuous veno-venous haemofiltration (CCVH). Improved baclofen clearance and the duration of mechanical ventilation in these patients were not compared to patients with no CCVH [22]. However, faster clearance of baclofen with RRT was already described in literature. Meulendijks et al. reported a decrease in half-life of 7.4 h to 4.8 h and Hsieh et al. a decrease in half-life of 15.7 h to 3.1 h [20,23]. In addition, Cleophax et al. had published a case of a severe baclofen-poisoned patient with preserved renal function treated with haemodialysis, and found a mean haemodialysis elimination half-life close to the value found before haemodialysis [24].

For the first time, a cohort study was done to compare the effect of RRT on the elimination half-life in a patient with normal renal function. In our cohort, for all RRT patients, it was set up with the aim of eliminating baclofen. Baclofen blood levels were significantly greater in the RRT patient group, which was probably the decision criteria for initiating RRT by the intensive care physicians and this is probably a bias in this study. We did not observe a decrease in the elimination half-life between patients who were undergoing RRT or not. Furthermore, the calculated half-lives were similar to those observed at therapeutic doses, from 3.5 h to 6.8 h [25] and thus were relatively short, contrary to a case report of increased half-life up to 34.5h for ingestion of 450 mg [21].

Since baclofen toxicity is essentially neurological, causing deep coma, the endpoint chosen to assess the clinical effectiveness of RRT was the duration of patient intubation. However, many complications such as inhalation pneumopathy can prolong this intubation time, which was the case for several patients and may present a bias. The two groups have significantly different initial baclofen levels. This may present a new bias in the comparison of duration of intubation. However, these baclofen levels were all collected at different times of intoxication. In our cohort, the lengths of mechanical ventilation were not significantly different between patients treated or not treated by RRT.

The clinical efficacy was not demonstrated in a case report of Meulendijks et al. Despite biological efficacy of haemofiltration, the patient woke up only after 40 hours, while serum concentrations were undetectable past 22 h [23]. Persistent neurological symptoms have also been described many times by various authors [24,22,26,27]. Indeed, we know that baclofen, which is moderately lipophilic, has a low diffusion in the cerebrospinal fluid. In animal studies, the apparent elimination

rate of nerve tissue is much slower than that of serum [28]. Furthermore, different authors observed plasma rebounds of baclofen, possibly related to a release from the CNS and lipid store, according to their assumptions [24,21,26,27]. In our study, included patients achieved one or more RRT at different times post-intoxication. The best delay for starting RRT is unknown but it could be a determining factor in its effectiveness.

Although the number of patients included in this study is small, it also reflects the small number of hospitals that can routinely perform baclofen assays. This limit should be borne in mind when interpreting the data. But it should also be remembered that the use of RRT is well documented in toxicology only in certain indications (e.g. ethylene glycol, lithium).

In conclusion, RRT did not appear to significantly increase baclofen clearance and providing clinical benefit in patients without renal impairment. In view of these results, RRT cannot be recommended systematically in the management of severe baclofen intoxication in these patients, considering the risks and complications associated.

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Figure 1: Schematic pharmacokinetic model structure. A 1-compartment model was constructed with a first order absorption rate constant (Ka) and a first order elimination rate constant (Ke). The delayed absorption process was described by Tlag and bioavailability by F. A(1) is the amount of baclofen in the central (plasmatic) compartment and V/F the apparent volume of distribution of the central compartment.

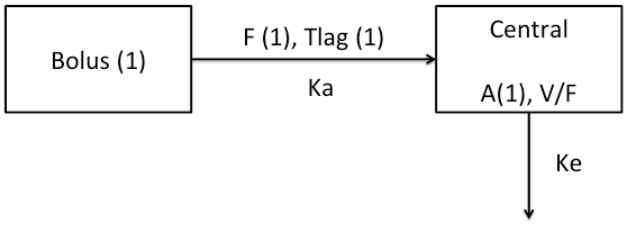

Figure 2: Scatter plot of the individual model-predicted concentrations *vs* observed concentrations.

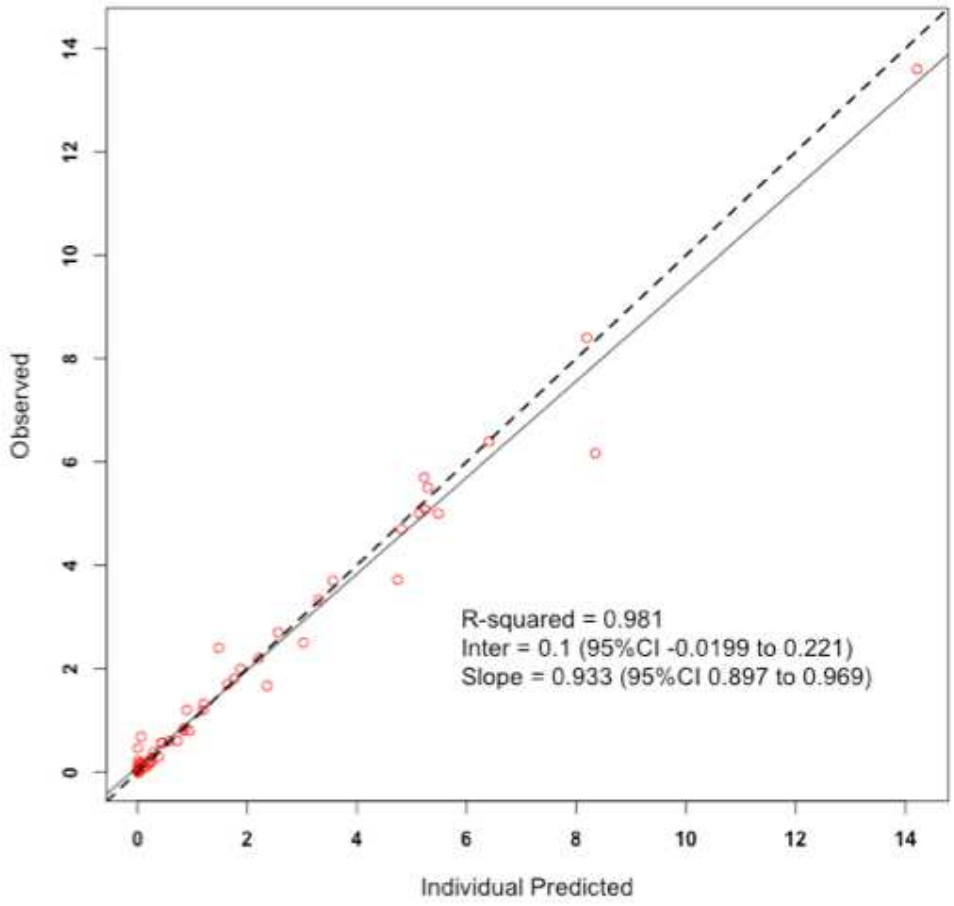

Figure 3: Weighted residuals versus predictions (left), and time (middle) and histogram of residuals with a superimposed normal curve (right).

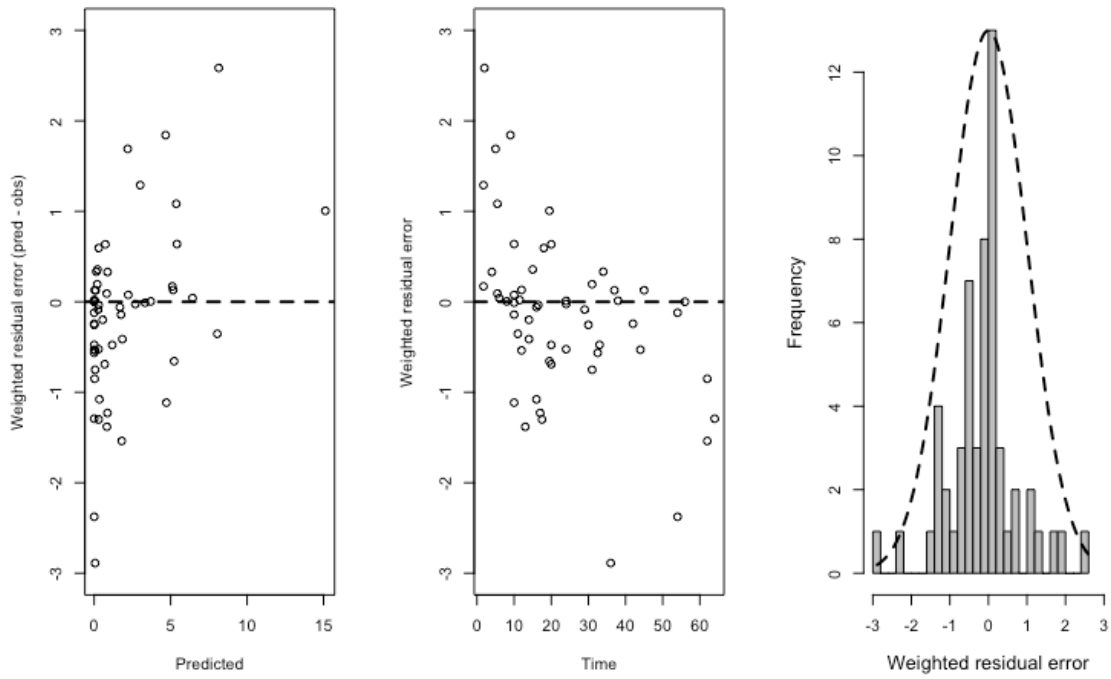

Table 1: Baclofen pharmacokinetic parameters in the studied population. SD, Standard deviation, F, bioavailability; Ka, absorption rate constant; Ke, elimination rate constant; V1/F, volume of distribution.

Parameter	Unit of measure	Final model parameter estimate Mean (SD)	Shrinkage (%)
F	-	0.61 (0.15)	9.74
Ka	h-1	0.71 (0.30)	35.8
Ke	h-1	0.32 (0.21)	18.6
V1/F	L	16.5 (3.64)	12.1
Lag time	h	1.58 (1.56)	34.7

Table 2: Median [IQR] of baclofen pharmacokinetic parameters and duration of intubation for patient with and without haemodialysis. Comparison of quantitative variables

	H**a**emodialysed patients Median [IQR]	Non-h**a**emodialysed patients Median [IQR]	*p*-value
Number of cases	6	19	
Estimated dose of baclofen (mg)	970 [500-1500]	350 [160-700]	NS
Initial baclofen level (mg/L)	5.4 [4.7-6.4]	1.75 [0.8-3.7]	S
Elimination half-life (h)	3.1 [2.2-4.8]	3.4 [1.4-5.5]	NS
Duration of intubation	72 [48-72]	72 [24-96]	NS