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Pharmacokinetics of Desethylamiodarone in the Rat after its Administration as the Preformed Metabolite, and after Administration of Amiodarone

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ABSTRACT: The pharmacokinetics of desethylamiodarone (DEA), the active metabolite of amiodarone (AM), were studied in the rat after administration of AM or preformed metabolite. Rats received 10 mg/kg of either intravenous or oral AM HCl or DEA base. Blood samples were obtained via a surgically implanted jugular vein cannula. Plasma concentrations were measured by a validated LC/MS method. In all AM treated rats, AM plasma concentrations greatly exceeded those of the formed DEA. The fraction of AM converted to DEA after i.v. administration was 14%. Amiodarone had a significantly lower (~50%) clearance than DEA, although the volume of distribution and terminal phase half-life did not differ significantly. The hepatic extraction ratio of DEA was 0.48, similar to that of AM (0.51). Oral AM demonstrated higher plasma *AUC* (5.6 fold) and higher C_{max} (6.1 fold) than oral DEA and oral bioavailability of AM (46%) was greater than DEA (17%). The estimated fraction of the oral dose of AM converted to DEA was 4.5 fold higher than after i.v. administration, suggesting first-pass formation of DEA from AM. Amiodarone and DEA differed in their pharmacokinetic characteristics mostly due to a higher *CL* of DEA. With oral dosing, AM appeared to undergo significant presystemic first-pass metabolism within the intestinal tract. Copyright © 2007 John Wiley & Sons, Ltd.

Key words: desethylamiodarone; sequential metabolism; amiodarone; pharmacokinetics

Introduction

Amiodarone (AM) is a potent broad spectrum antiarrhythmic drug, which exerts its actions through multiple mechanisms including potassium and calcium channel suppression and ß-adrenoreceptor blockage [1,2]. Amiodarone is used for prophylactic and direct alleviation of a wide range of cardiac rhythm disturbances. Unlike some other antiarrhythmic agents, AM can reduce the risk of mortality in patients with severe congestive heart failure or after acute myocardial infarction [3]. As is the case for most drugs, the adverse effects can limit its clinical utility. Chronic administration of AM is associated with a wide range of toxic side effects in a variety of tissues including liver [4], lung [5], thyroid [6] and pancreas [7]. Plasma concentration monitoring for AM can be a useful adjunct in clinical practice, as a narrow therapeutic range for the drug has been proposed (0.5–2.0 mg/l in plasma) [8].

Amiodarone has a complex pharmacokinetic profile. It has erratic unpredictable absorption and low bioavailability. Amiodarone also possesses a high volume of distribution and as a consequence, a corresponding long elimination half-life [9,10]. Amiodarone is extensively metabolized and has a low hepatic extraction ratio in humans [9], but moderate hepatic extraction ratio in rats [11]. Metabolism of AM is predominantly accomplished in the liver, although there is evidence for

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extrahepatic metabolism in some preclinical species [12]. Among the five pathways involved in the metabolism of AM (*N*-deethylation, hydroxylation, *O*-dealkylation, deiodination and glucuronidation), *N*-dealkylation is the most important [13,14]. The immediate product of this metabolic pathway is desethylamiodarone (DEA), which is the main circulating metabolite of AM in humans and rats [12,15]. It has been shown that DEA shares some of the pharmacological and toxicological properties of the parent drug in heart and lung. For instance, DEA significantly increases the action potential duration and decreases the maximum rate of depolarization at clinically relevant concentrations [2]. Also, DEA shows substantial effects on myocardial fast ion channels [16] and DEA has been shown to be more toxic than AM in pulmonary cell types, suggesting its important role in the development of pulmonary fibrosis induced by AM [2].

Based on the pharmacological importance of DEA in AM therapy, the pharmacokinetic and metabolic fate of DEA is of clinical relevance. Although the lipophilic structure of DEA confers some pharmacokinetic properties similar to the parent drug, the available data regarding the pharmacokinetics of DEA are limited. The only report confines the sole administration of DEA to the intraperitoneal route in the rat [17]. There are no reports, however, of the pharmacokinetics of preformed DEA after intravenous (i.v.) or oral administration. Therefore clearance (*CL*) and volume of distribution (V_{dss}) of DEA in both human and experimental animals have not been reported. This information would assist in understanding why the plasma concentrations of DEA, while measurable, are very low after administration of parent drug to rat, a species that was used to study the effects of hyperlipidemia on pharmacokinetics [10,18]. Therefore the main objective of the current study was to characterize the pharmacokinetic profile of DEA following oral and i.v. administration of both parent drug and the preformed metabolite in the rat.

Methods

Chemicals

Amiodarone HCl and ethopropazine HCl were obtained from Sigma (St Louis, MO, USA). Desethylamiodarone was a kind gift from Wyeth-Ayerst Research (Princeton, NJ). Methanol, acetonitrile, hexane, water (all HPLC grades), dimethyl sulfoxide (DMSO) and formic acid 88% were purchased from Fisher Scientific (Fair Lawn, NJ, USA). Isoflurane USP was purchased from Halocarbon Products (River Edge, NJ, USA). Heparin sodium for injection 1000 units/ml was obtained from Leo Pharma Inc. (Thornhill, Ontario, Canada). Amiodarone HCl as a sterile injectable solution (50 mg/ml) was purchased from Sandoz (Sandoz Canada, PQ, Canada).

Animals and experimental procedures

All experimental protocols involving animals were approved by the University of Alberta Health Sciences Animal Policy and Welfare Committee. A total of 18 male Sprague-Dawley rats (Charles River, PQ, Canada) were used in this study. The body weight was 250–350 g and all the rats were housed in temperature controlled rooms with 12 h light per day. The animals were fed a standard rodent's chow containing 4.5% fat (Lab Diet® 5001, PMI Nutrition LLC, Brentwood, USA). Free access to water was permitted prior to experimentation but food was withheld overnight prior to experimentation.

The day before the experiment, the right jugular veins of all rats were catheterized with Micro-Renathane tubing (Braintree Scientific, Braintree, MA) under isoflurane anesthesia. The cannula was filled with 100 U/ml heparin in 0.9% saline. After implantation, the animals were transferred to regular holding cages and allowed free access to water, but food was withheld overnight. The next morning the rats were transferred to metabolic cages and dosed with AM or DEA.

Drug administration and sample collection

Amiodarone i.v. dosing solution was prepared by dilution of AM HCl injectable solution in normal saline (7.14 mg/ml). Intravenous injection of DEA (30 mg/mL) was made up in DMSO: dextrose 5% (10:90). The total amount of DMSO injected was 1/25th the concentration known to influence cytochrome P450 activity of liver [19].

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The DEA dosing solution was kept warm at 40°C until drawn into the syringe and injected; failure to do so caused a precipitate to form in the solution. For oral administration, AM HCl (4.5 mg/ml) and DEA (6 mg/ml) were prepared by dispersion of the powdered compounds in 1% methylcellulose.

On the morning of pharmacokinetic study, two groups of rats ($n = 5$ in each group) received i.v. doses of either 10 mg/kg of AM HCl or DEA base. The i.v. doses were injected over 60 s via the jugular vein cannula, immediately followed by injection of approximately 1 ml of sterile normal saline solution. Rats in the third and fourth groups ($n = 4$ each) received 10 mg/kg of AM HCl or DEA base suspension by oral gavage, respectively. In the i.v. dosed rats, at the time of first sample withdrawal, the first 0.2 ml volume of blood was discarded. This procedure was shown to have a negligible effect on the area under the plasma concentration versus time curve (*AUC*) in rats [20]. Food was provided to the animals 3 h after the dose had been administered.

In the rats given either AM or DEA i.v., blood samples (0.2–0.3 ml) were collected from the cannula at approximately 0.08, 0.33, 0.67, 1, 2, 3, 4, 6, 8, 10, 24, 32, 48 h after dosing. In the rats given either AM or DEA orally, blood samples were collected from the cannula at approximately 0.5, 1, 2, 3, 4, 6, 8, 10, 24 and 48 h postdose. Heparin in normal saline (100 U/ml) was used to flush the cannula after each collection of blood samples. After collection, each blood sample was centrifuged at 2000*g* for 3 min. The plasma was transferred to new polyethylene tubes and stored at −30°C until assayed for AM and DEA.

Blood:plasma ratio

Known amounts of AM and DEA were dissolved in methanol in glass test tubes containing freshly obtained rat blood. The volume of methanol added was 15 µl/ml of blood. Two concentrations of AM were present in the tubes (~3000 and 150 ng/ml). For DEA, a concentration of 80 ng/ml was added. The tubes were placed in a shaking water bath at 37°C for 1 h. At that time the tubes were removed from the bath and 100 µl of blood was transferred to microcentrifuge tubes. The remaining blood was centrifuged at 2500*g* for 10 min. A volume of 100 µl of the plasma layer was transferred to microcentrifuge tubes. The tubes were assayed for AM and DEA. The mean blood *CL* of AM and DEA were estimated by dividing the respective mean plasma *CL* by the corresponding blood to plasma ratios. Hepatic extraction ratios (*E*) were estimated, assuming negligible extrahepatic *CL*, by taking the quotient of *CL* in blood divided by average hepatic blood flow of 55.2 ml/min/kg [21].

Assay

Measurements of AM and DEA were accomplished in each plasma sample by LC/MS as described previously [22]. The validated lower limit of quantitation was 2.5 ng/ml for both AM and DEA, based on 0.1 ml of plasma.

Data analysis

Noncompartmental methods were used to calculate the pharmacokinetic parameters. The elimination rate constant (λ_z) was estimated by subjecting the plasma concentrations in the terminal phase to linear regression analysis. The terminal elimination phase half-life ($t_{1/2}$) was calculated by dividing 0.693 by λ_z. The concentration at time 0 h after i.v. dosing was estimated by back extrapolation to time zero using the first two measured log-transformed concentrations (5 min and 20 min) after dosing. The $AUC_{0-\infty}$ after dosing was calculated using the combined log-linear trapezoidal rule from time 0 h postdose to the time of the last measured concentration, plus the quotient of the last measured concentration divided by λ_z. Clearance (*CL*) was calculated as $CL = Dose/AUC_{0-\infty}$, and the steady-state volume of distribution (V_{dss}) was calculated as $V_{dss} = CL \times AUMC/AUC$, where *AUMC* is the area under the first moment plasma concentration vs time curve, from time of dosing to infinity.

The oral bioavailability assuming linear kinetics was calculated as follows

$$F = \frac{\text{mean } AUC_{oral} \times Dose_{iv}}{\text{mean } AUC_{iv} \times Dose_{oral}}$$

The maximum plasma concentration (C_{max}) and the time at which it occurred (t_{max}) were

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determined by visual examination of the data, assuming linear kinetics for AM and DEA. The fraction of AM converted to DEA (f_m) after the i.v. and oral administration of AM was determined using the following equations [23,24]

$$fm_{iv} = \frac{AUC^{DEA}_{AM,iv} \times Dose_{DEA,iv}}{AUC^{DEA}_{DEA,iv} \times Dose_{AM,iv}} \quad \text{and}$$

$$fm_{oral} = \frac{AUC^{DEA}_{AM,oral} \times Dose_{DEA,oral}}{AUC^{DEA}_{DEA,oral} \times Dose_{AM,oral}}$$

where AUC^{DEA}_{AM} and AUC^{DEA}_{DEA} are the mean $AUC_{0-\infty}$ of DEA after administration of AM or preformed DEA, respectively. The calculation of fm_{oral} assumes that the bioavailability of metabolite after parent drug is the same as that of preformed metabolite.

Statistical analysis

Compiled data were reported as mean $\pm$ SD, unless otherwise indicated. Differences were assessed for significance using paired or unpaired Student's *t*-test as appropriate. The level of significance was set at $\alpha = 0.05$.

Results

After i.v. dosing, the plasma concentrations of AM and preformed DEA declined in a manner consistent with multicompartmental pharmacokinetics (Figure 1). Although the concentrations of AM and preformed DEA were initially similar immediately after dosing, within 3 h they began noticeably to diverge, with the measured concentrations of the AM becoming higher than those of the preformed DEA. The plasma concentrations of DEA formed from i.v. administration of AM were much lower than those of AM or preformed DEA. There was evidence of a secondary DEA peak occurring at approximately 3 h after administration of AM. The mean concentrations during the terminal phase appeared to decline in a similar manner for AM and DEA (preformed or formed from AM).

With the oral administration of 10 mg/kg of AM (Figure 1), DEA was observed in plasma in all of the rats by the time of the first blood sample (0.5 h). In the post-absorptive phase, the plasma concentration profiles of DEA were similar to those of parent drug, albeit with much lower concentrations (Figure 1). Following the oral administration of preformed DEA, the concentration versus time curve of DEA showed a close resemblance to that of parent drug during the absorption and distribution phases. During the terminal elimination phase, however, the preformed DEA concentrations appeared to decline more rapidly than did the concentrations of AM and DEA formed from AM. By 48 h postdose, the plasma concentrations of preformed DEA were

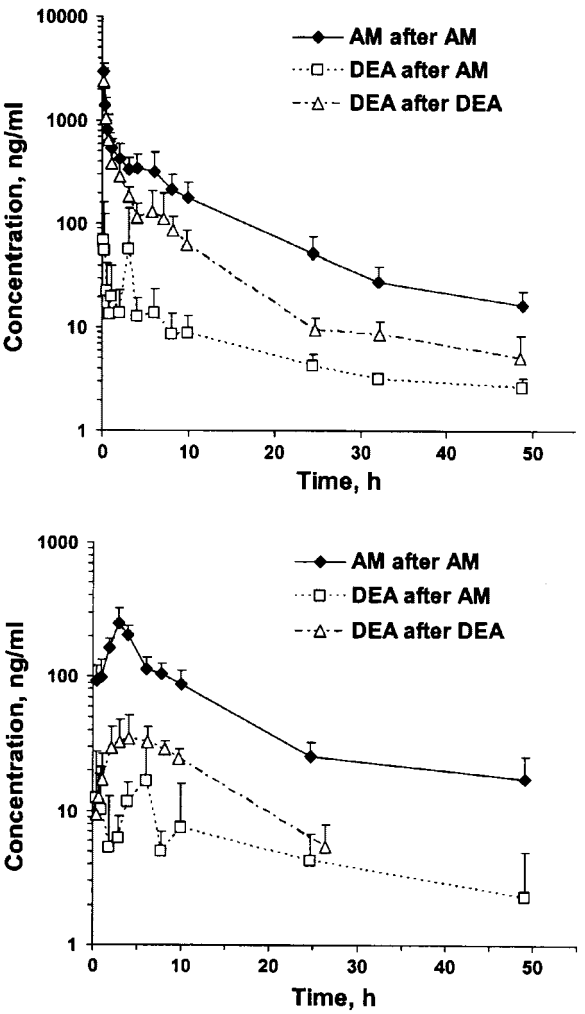

Figure 1. Plasma concentration versus time curves of amiodarone and desethylamiodarone (mean $\pm$ SD) following the intravenous (top panel) or oral (lower panel) administrations of 10 mg/kg of either amiodarone HCl or desethylamiodarone base to Sprague-Dawley rats

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Table 1. Mean ± SD (range in parentheses) of pharmacokinetics of amiodarone (AM) and desethylamiodarone (DEA) in Sprague-Dawley rats

	Intravenous (AM) 10 mg/kg ($n = 5$)	Intravenous (DEA) 10 mg/kg ($n = 5$)	Oral (AM) 10 mg/kg ($n = 4$)	Oral (DEA) 10 mg/kg ($n = 4$)
Amiodarone kinetics				
$AUC_{0-tlast}$ (mg h/l)	6.44 ± 2.27[a] (4.70–9.22)	–	2.61 ± 0.445[b] (2.17–3.21)	–
AUC_{0-inf} (mg h/l)	6.95 ± 2.26[a] (11.7–40.5)	–	3.18 ± 0.558[b] (2.50–3.86)	–
$t_{1/2}$ (h)	21.6 ± 11.0 (11.7–40.5)	–	20.3 ± 9.73 (9.80–33.4)	–
CL (ml/h/kg)	1559 ± 461[a] (1040–2035)	–	–	–
V_{dss} (ml/kg)	21.4 ± 8.02 (13.1–30.7)	–	–	–
C_{max} (ng/ml)	–	–	251 ± 75.9[b] (190–361)	–
t_{max} (h)[e]	– –	–	2.9 (2.9–4.0)	
CL/F (ml/h/kg)	–	–	3046 ± 556[b] (2452–3795)	–
Desethylamiodarone kinetics				
$AUC_{0-tlast}$ (mg h/l)	0.365 ± 0.149[c] (0.175–0.531)	3.15 ± 1.09 (1.98–4.92)	0.218 ± 0.120 (0.107–0.382)	0.549 ± 0.117 (0.415–0.682)
AUC_{0-inf} (mg h/l)	0.459 ± 0.118[c] (0.314–0.623)	3.38 ± 1.37 (2.01–5.68)	0.346[d]	0.567 ± 0.122 (0.421–0.694)
$t_{1/2}$ (h)	36.7 ± 13.0 (21.9–54.9)	27.9 ± 28.7 (11.3–78.9)	22.5[d]	9.39 ± 1.69 (7.87–11.8)
CL (ml/h/kg)	–	3307 ± 1153 (1762–4969)	–	–
V_{dss} (ml/kg)	–	28.7 ± 16.1 (18.8–58.8)	–	–
C_{max} (ng/ml)	–	–	20.9 ± 11.8 (12.5–37.9)	40.9 ± 12.9 (30.1–59.0)
t_{max} (h)[e]	–	–	6.0 (6–10)	4.1 (2.0–6.2)
CL/F (ml/h/kg)	–	–	–	18316 ± 4175 (14404–23746)

[a] Denotes significant difference between i.v. AM and preformed DEA given i.v.
[b] Denotes significant difference between oral AM and preformed DEA given orally.
[c] Denotes significant difference between i.v. preformed DEA and formed DEA after AM given i.v.
[d] $n = 2$ ($t_{1/2}$ not determinable in all rats).
[e] Median value (range in parentheses).

below the validated lower limit of quantitation of the assay (Figure 1, lower panel).

After i.v. administration the AM concentrations as reflected by *AUC* were significantly higher for the AM than preformed DEA (Table 1). This translated into a significantly higher *CL* for DEA compared with AM. On the other hand, there was no significant difference between AM and DEA in the V_{dss} or the terminal phase $t_{1/2}$. The *AUC* of DEA formed after i.v. administration of AM was significantly lower than that of DEA administered i.v. as preformed metabolite. However the $t_{1/2}$ of preformed DEA given i.v. and DEA formed from i.v. AM were not different.

The oral administration of AM yielded a similar finding to i.v. administration, in that the *AUC* of AM was significantly higher (~5.6 fold) than that of preformed DEA given orally. This was also reflected in the observed C_{max}, in which concentrations of AM were significantly higher (~6.1 fold) than preformed DEA. The t_{max} after

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oral dosing observed for the preformed DEA was similar to that of AM, suggesting a similar rate of absorption for these two compounds. In contrast to i.v. administration, the *AUC* of DEA formed from oral AM was similar to that of preformed DEA given orally. Although the mean $t_{1/2}$ of AM was higher than that of preformed DEA given orally, there was much variability and the difference was not significant. Similarly, after oral administration the $t_{1/2}$ of DEA formed from AM was not significantly different from preformed DEA (Figure 1, Table 1). After 24 h, the preformed DEA concentrations were below the lower limit of quantification of the assay.

The oral bioavailabilities of AM and DEA were estimated to be 46% and 16.8%, respectively. The fm_{iv} for DEA was calculated to be 14.3%. In contrast, the fm_{oral} (64.1%) was much higher.

The mean blood:plasma ratios of AM were similar for both the high (0.88 ± 0.029) and low (0.98 ± 0.064) concentrations. The mean blood:-plasma ratio for DEA was significantly higher (2.1 ± 0.18) than both measurements observed for AM.

Discussion

Previously only very low circulating concentrations of DEA were observed in plasma after administration of AM to rats [10,12,25]. This could be due to very high *CL* of DEA compared with AM, minimal formation of DEA from AM, or a combination of both. The present study is the first to report the pharmacokinetics of preformed DEA following i.v. or oral administration in rats. These routes were chosen, in conjunction with dosing of AM and assay of parent drug and metabolite, to permit an understanding of the fraction of the dose of AM that is converted to DEA, and the relative *CL* of AM and DEA. The *CL* of DEA was significantly greater than that of AM, in part explaining the low plasma concentrations of the metabolite compared with the parent drug in the rat. It was also found that less than 15% of the dose of i.v. AM is converted to DEA. Thus it is apparent that both rapid *CL* of DEA and limited formation of DEA from AM are responsible for the low plasma concentrations of DEA after i.v. AM. Although the *CL* differed between AM and DEA, there was no significant difference between the V_d, which is indicative of extensive distribution to the tissues for both compounds.

In our previous paper examining amiodarone kinetics it was had reported that the hepatic extraction ratio was at most 0.72 [20]. Our calculation was only valid if penetration of drug into blood cells was negligible. However, the results of the blood binding experiment indicated that there was a modest degree of uptake of AM and extensive uptake of DEA into blood cells; similar findings had been reported previously [25]. These data can be used to convert our plasma *CL* values to blood *CL* by dividing the plasma *CL* by the blood:plasma ratios, thus yielding mean blood *CL* of 1676 and 1575 ml/h/kg for AM and DEA, respectively. The mean hepatic blood flow in rat has been estimated to be 3312 ml/h/kg. Assuming that the majority of the clearance of AM and DEA are attributable to the liver, the hepatic extraction ratios would be at most 0.51 and 0.48, respectively, both values being indicative of compounds possessing a moderate hepatic extraction ratio.

The determination of *fm* indicated that a greater fraction of the dose was converted to metabolite when the drug was administered via the oral route. This suggested that there was a significant amount of the dose of AM converted to DEA within the intestinal tissues upon the first pass. It should be recognized, however, that the calculation of fm_{iv} assumes that there is no substantial degree of sequential metabolism of DEA, something we could not verify in the current study. It is of note that AM has been shown to be metabolized to DEA by intestinal microsomal preparations, further supporting the notion of significant intestinal first pass metabolism [12]. Recently in the human Caco-2 it was shown that DEA was a substrate for the ATP-binding cassette transporter [27]. Such a mechanism could also potentially contribute to a low oral bioavailability of DEA in the rat.

In our previous studies in the male Sprague-Dawley rat single 25 mg/kg i.v. and 50 mg/kg oral doses were administered. Therefore the results of our current and previous studies can

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be compared to examine the influence of dosing rate on the pharmacokinetics of AM [10,12]. Similar values of *CL* were observed from the i.v. data of 25 mg/kg (1378 ml/h/kg) and 10 mg/kg dose levels (Table 1; $p>0.05$). On the other hand, there were significantly higher values of V_{dss} (2.2-fold higher) and $t_{1/2}$ (2-fold higher) with 25 mg/kg compared with the 10 mg/kg dose levels (Table 1: $p<0.05$) [20]. In rats given even higher single doses of 50 mg, a similar trend in increasing terminal $t_{1/2}$ and V_{dss} was observed, in which values of 131 h and 72 l/kg were observed, respectively [28]. It is possible that we have underestimated the true terminal phase $t_{1/2}$ due to our duration of sampling, which was limited to 48 h. However, given the trend of increasing terminal phase $t_{1/2}$ with increasing dose across these studies, perhaps a more feasible explanation is saturation of plasma protein binding of AM at higher doses. This is in line with previous data in which as the dose level increased, a progressive increase was noted in the rat blood to plasma concentration ratios for AM [25].

Similar to i.v. doses, the single dosing of rats with 10 and 50 mg/kg of oral AM HCl showed a nearly proportionally (4.5-fold) higher AM *AUC* in the 50 mg/kg dose group (Table 1) [20]. Oral *CL* (*CL/F*) showed comparable results (Table 1) with the previous results (3496 ml/h/kg) suggesting linear pharmacokinetics in plasma at the oral dose levels of 10 and 50 mg/kg of AM [20]. In the current study (Table 1), the $t_{1/2}$ of AM after oral doses was significantly lower (58.6% lower) than observed with 50 mg/kg. The C_{max} was 62% lower with 10 mg/kg versus 50 mg/kg doses ($p<0.05$). The lower dose of 10 mg/kg of AM HCl was associated with a mean oral bioavailability which was higher (47%) than that previously estimated for higher doses of 50 mg/kg (35%) in the fasted state, suggesting that the absorption of the dose was more efficient with smaller dose levels.

Given the *fm* values after oral and i.v. dosing, it is clear that AM is biotransformed in the rat to other metabolites beyond DEA. It was of note that in the LC/MS scans of the injected plasma samples, there was evidence of ions with $m/z = 635.3$, consistent with 3-hydroxy-monodesethylamiodarone. This is a metabolite of DEA previously identified by other investigators in both human and rat plasma [29,30]. This metabolite has also been identified in liver, heart, lung and kidney of rats receiving AM [29]. Furthermore, it was the major metabolite of DEA after incubation of DEA with rabbit microsomes [29]. Unfortunately, the measurement of this hydroxylated metabolite, or other metabolites of AM, in rat plasma was not possible due to the unavailability of standard compound.

The terminal $t_{1/2}$ of AM in humans given repeated doses has been estimated to be much larger (>50 days) than what we and others have observed in rat, reflecting a larger V_d and slower *CL* of the drug in humans [9,31]. In human subjects, the circulating concentrations of DEA are much higher than those in the rat. For example, in 30 healthy fasted subjects given AM as tablets 600 mg orally, the DEA/AM ratio of *AUC* was 1.26 [31]. This ratio, however, does not differentiate between the *CL* of DEA and the formation of DEA from AM. Nevertheless, irrespective of the cause of the higher DEA levels in humans, it is clear that the significant plasma concentrations of DEA must be taken into account for its possible pharmacological effects as contributions towards the therapeutic and/or toxicological potencies in clinical use.

In conclusion, AM and DEA showed different pharmacokinetic characteristics within the rat. Desethylamiodarone has a higher systemic clearance than the parent drug, thus contributing to the low plasma concentrations observed after i.v. and oral dosing. Only about 1/7th the dose of AM was apparently converted to DEA after i.v. dosing in the rat. In contrast, upon oral dosing with AM, a much higher fraction of the dose seems to be biotransformed to DEA.

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