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Evaluation of the potential of ion pair formation to improve the oral absorption of two potent antiviral compounds, AMD3100 and PMPA

J. Van Gelder [a,1], M. Witvrouw [b,1], C. Pannecouque [b], G. Henson [c], G. Bridger [c], L. Naesens [b], E. De Clercq [b], P. Annaert [a], M. Shafiee [a], G. Van den Mooter [a], R. Kinget [a], P. Augustijns [a,*]

[a] *Laboratorium voor Farmacotechnologie en Biofarmacie, Campus Gasthuisberg, O & N, B-3000 Leuven, Belgium*
[b] *Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000, Leuven, Belgium*
[c] *AnorMED, Langley, British Columbia, V2Y1N5, Canada*

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Abstract

9-(2-phosphonyomethoxypropyl)adenine (PMPA) and AMD3100 are highly potent and selective antiretroviral agents. Since PMPA is negatively charged and AMD3100 positively charged at physiological pH, their transepithelial transport and their potential for oral drug delivery is very low. In this study, ion pair formation was evaluated as a possible strategy to enhance transepithelial transport of PMPA and AMD3100. Positively charged counter ions such as *t*-hexyl-, *t*-heptyl-, *t*-octylammonium bromide and dodecyl-, tetradecyl-, hexadecyltrimethylammonium bromide were used to form ion pairs with PMPA, while sodium taurodeoxycholate (in vitro experiments) and sodium taurocholate (in vivo experiments) were used as counter ions for AMD3100. The effect of counter ions on transepithelial transport of PMPA (1 mM) and AMD3100 (1 mM) was investigated by measuring the flux across Caco-2 monolayers. An enhancement in drug transport could be observed at a concentration of 2 mM of hexadecyltrimethylammonium bromide (counter ion for PMPA) and 10 mM of sodium taurodeoxycholate (counter ion for AMD3100), but at the concentrations used, the absorption enhancing effect could be attributed to a reduction of the integrity of the monolayers. When AMD3100 transport was tested at a concentration of 200 μM, no flux was observed, even in the presence of relatively high concentrations of counter ion (20 times the concentration of AMD3100). Results obtained from partitioning studies of the drugs in the presence or absence of counter ion revealed that competition by other ions was responsible for the absence of an effect: when pure water was used as the aqueous phase, a reduction up to $24.4 \pm 1.4\%$ and $17.0 \pm 1.3\%$ of the initial aqueous concentration was observed for PMPA and AMD3100, respectively; however, as soon as other ions were present in the aqueous phase, the effect of the counter ion was diminished (25–50 mOsm) or completely abolished (270–305 mOsm). The absorption enhancing effect of counter ions was also studied in vivo: pharmacokinetic studies in rabbits showed that the oral bioavailability

* Corresponding author. Tel.: +32-16-345829; fax: +32-16-345996.
E-mail address: patrick.augustijns@med.kuleuven.ac.be (P. Augustijns)
[1] Both authors are equally important.

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of AMD3100 in the presence of 4 equivalents of taurocholic acid remained very low and was only 3.2-fold better (i.e. 3.6%) in comparison to pure AMD3100. In view of the results obtained in the Caco-2 system, this absorption enhancement can be attributed to an effect on monolayer integrity rather than to the potential to form ion pairs. We can conclude that the formation of ion pairs may not be very efficient as a strategy to enhance transepithelial transport of charged hydrophilic compounds, as competition by other ions may abolish the beneficial effect of counter ions.

Keywords: Ion pairs; Transport; Caco-2; Absorption enhancer; Antiviral

1. Introduction

AMD3100, a bicyclam derivative (De Clercq et al., 1992, 1994; De Vreese et al., 1996), and 9-(2-phosphonolmethoxypropyl)adenine (PMPA), an acyclic nucleoside phosphonate analogue (Balzarini et al., 1993; De Clercq, 1997) are highly potent and selective antiretroviral agents which are currently undergoing phase I and II clinical trials in humans infected with human immunodeficiency virus (HIV), respectively. For chronic treatment, oral administration would be the preferred route of these compounds. However, both compounds suffer from low absorption after oral administration, mainly due to their hydrophilic character: at physiological pH, PMPA is negatively charged, while AMD3100 is a tetracation. Therefore, their ability to cross the epithelial barrier is very low. For PMPA, a prodrug in which the charges are masked has already been developed as a strategy to enhance the oral bioavailability (Naesens et al., 1998), while for AMD3100, no prodrugs are available yet. A possible alternative to enhance the transmembrane transport of AMD3100 and PMPA would be to mask the charges that are mainly responsible for the hydrophilic character of the compound by using amphiphilic counter ions of opposite charge (Jonkman and Hunt, 1983; Neubert, 1989a). Several positively charged counter ions were used for PMPA (cetrimides, tetraalkylammonium bromides), while taurodeoxycholic acid (in vitro studies) and taurocholic acid (in vivo studies) were used as counter ions for AMD3100. The transepithelial transport of the drug candidates was evaluated in an in vitro model of the intestinal mucosa, Caco-2 (Hidalgo et al., 1989), in the absence or presence of counter ions. Ion pair formation was also studied using partitioning studies between *n*-octanol and different aqueous media. In addition, in vivo pharmacokinetic studies of AMD3100 after oral administration in the presence and absence of taurocholic acid were performed in rabbits to evaluate the effect of the presence of counter ions. Our results show that ion pair formation may be inefficient as a strategy to enhance the transepithelial transport of PMPA and AMD3100, as competition with other ions present in the medium limits the efficiency of ion pair formation between the respective drug and counter ion.

2. Materials and methods

2.1. Materials

PMPA was obtained from Gilead Sciences (Foster City, CA); AMD3100 was synthesized at AnorMED Inc. (Langley, British Columbia, Canada). Tetrabutylammonium hydrogen sulfate (Fluka, Switzerland), potassium dihydrogenphosphate (Merck, Darmstadt, Germany) and acetonitrile (Biosolve Ltd., The Netherlands) were HPLC grade. All chemicals used for cell culturing were purchased from Gibco Inc. (Life Technologies, Belgium). D-(+)-glucose, taurodeoxycholic acid (sodium salt), taurocholic acid (sodium salt), tetrahexyl-, tetraheptyl- and tetraoctylammonium bromide were purchased from Sigma (St. Louis, MO). Dodecyltrimethyl-, tetradecyltrimethyl- and hexadecyltrimethylammonium bromide were kindly provided by Professor E. Roets [Laboratory of Pharmaceutical Chemistry (K.U.Leuven, Leuven, Belgium)] (Paesen et al., 1994). Transport medium (TM) consisted of 500 ml Hanks' Bal-

anced Salt Solution (HBSS) containing 25 mM glucose and 10 mM Hepes.

2.2. HPLC analysis of PMPA and AMD3100

PMPA and AMD3100 were analyzed using a high-performance liquid chromatographic system equipped with a model 600E Controller and Pump, a model 717plus autosampler and a model Lambda-Max UV detector at 260 nm and 220 nm for PMPA and AMD3100, respectively (Waters, Milford, MA). UV signals were monitored and the obtained peaks integrated using Waters Maxima 820 chromatography software.

For PMPA, the column used was a Waters SymmetryShield C8 (4.6 × 150 mm i.d., 5 μm particle size). The mobile phase consisted of a buffer [10 mM potassium dihydrogenphosphate and 2 mM tetrabutylammonium hydrogensulfate adjusted to pH 5.5 with ammonia 2.5%] containing 7% (v/v) acetonitrile. Separation was carried out in the isocratic mode. The flow rate was 1 ml/min and the volume injected was 50 μl.

For the analysis of AMD3100, a homepacked poly(styrene-divinylbenzene) column (5 × 0.46 cm i.d., 8 μm particle size, 100 nm pore size; PLRPS, Polymer Labs, The Netherlands) was used. Mobile phase A consisted of NaOH 0.1 N, while mobile phase B consisted of acetonitrile. Separation was carried out using a gradient method starting at 80% mobile phase A, followed by a linear change to 65% mobile phase A over 4 min, immediately returning to the initial conditions. The flow rate was 1 ml/min and the volume injected was 50 μl. Total analysis took 8 min.

2.3. Caco-2 cell culture

Caco-2 cells were kindly provided by Dr Y. Schneider (UCL, Louvain-La-Neuve, Belgium). Cells were grown in 75 cm^2 culture flasks at 37°C in an atmosphere of 5% CO_2 and 90% relative humidity. Cells were passaged every 3–4 days (at 70–80% confluence) at a split ratio of 1 to 7. The Caco-2 cells were maintained in Dulbecco's Minimum Essential Medium containing high glucose (4.5 g/l), glutaMAX™, 100 U/ml of penicillin, 100 mg/ml of streptomycin, 1% non essential amino acids and 10% fetal bovine serum and were grown in tissue culture flasks (75 cm^2, Nunc, Roskilde, Denmark). Cells were negative for Mycoplasma infection. For transport experiments, Caco-2 cells were plated at a density of 60 000 cells/cm^2 on Transwell membrane inserts (3 μm pore diameter, 12 mm diameter; Corning Costar Corporation, Cambridge, MA). Confluence was reached within 3–4 days after seeding and the monolayers were used for experiments between days 23–25 post-seeding. Cells between passage number 115 and 142 were used in the experiments. Apical (AP) and basolateral (BL) chamber volumes were maintained at 0.5 and 1.5 ml, respectively. Transepithelial electrical resistance (TEER) was measured using an EVOM Voltohmmeter (WPI, Aston, England). Only monolayers having initial TEER values above 200 ohm·cm^2 were used in studies. Sodium fluorescein was used as a hydrophilic marker for cell monolayer integrity. Typical sodium fluorescein flux values across Caco-2 monolayers after the transport experiments with test compound were below 0.5% per h.

2.4. Transepithelial transport studies

For the determination of the transepithelial flux of PMPA and AMD3100 across Caco-2 monolayers, the polarized monolayers were preincubated with transport medium (TM) for 30 min, after which TEER values were measured to check cell monolayer integrity. The medium was then replaced by TM with test compound (200–1000 μM) at the donor side in the presence or absence of counter ions. Samples were taken from the apical and basolateral side (100 μl), and the volume withdrawn was replaced with fresh transport medium, which was corrected for in further calculations. All flux experiments were conducted in triplicate. Transport was expressed as concentrations appearing at the receptor side.

2.5. Partitioning studies

The influence of ion-pair formation with PMPA and AMD3100 was evaluated by partitioning PMPA and AMD3100 for 1 h between *n*-octanol and an aqueous phase (equal volumes for PMPA

and 9:1 *n*-octanol:water for AMD3100) in the presence or absence of counter ions. Aqueous phases used were pure water, NaCl 25–50 mOsm and TM 270–305 mOsm. All solutions were mutually saturated before starting the experiments. After separation of the two phases by centrifugation, the drug concentrations in the aqueous phases were determined by HPLC. The amount disappearing from the aqueous phase was considered as partitioned into the n-octanol phase.

2.6. Pharmacokinetic studies in rabbits

AMD3100 was administered intravenously (i.v.) or perorally (p.o.). For the in vivo experiments, taurocholic acid was used instead of taurodeoxycholic acid; preliminary partitioning studies had indicated that taurocholic acid is similarly effective as an ion-pairing agent as taurocholic acid, while taurodeoxycholic acid has been reported to be more toxic (Swenson et al., 1994) than taurocholic acid. Rabbits (weight of approx. 1 kg) received 2.5 mg/kg AMD3100 by intravenous bolus injection (ear vein) or 250 mg/kg AMD3100 in the presence or absence of 4 equivalents of taurocholic acid (648 mg taurocholic acid per 250 mg AMD3100) by oral gavage (via gastric intubation). Blood was drawn from the other ear vein at different time points, ranging from 2.5 min to 24 h after administration. Blood samples were collected at room temperature and kept at 4°C for a period of 12 h, after which the serum was collected. The samples were stored at −20°C until assayed. The AMD3100 concentration in the serum was determined using a bio-assay based on the 50% effective concentration (EC_{50}) of AMD3100 required to inhibit HIV-1 (III_B)-induced cytopathicity in MT-4 cells (Witvrouw et al., 1990) with an EC_{50} of 0.01 μg/ml. Briefly, 50 μl containing 100 $CCID_{50}$ of HIV-1(III_B) were transferred to microtitre tray wells containing serial dilutions of the serum samples (highest dilution 1/20). MT-4 cells were suspended in culture medium at 6×10^5 cells/ml and added to microtitre tray wells (50 μl cell suspension per well). After a 5 day incubation at 37°C, the number of viable cells was assessed by the MTT [3′-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method as previously described (Pauwels et al., 1988). Concentrations of AMD3100 in the rabbit serum samples were determined by comparison of their EC_{50} with the EC_{50} values of the compounds tested as such or in the presence of approximate dilutions of control serum. The presence of rabbit serum had no influence on the recovery of biologically active drug (data not shown). Taurocholic acid only inhibited HIV-1 (III_B) replication by 50% (EC_{50}) at a concentration of 463 μg/ml without being toxic for the MT-4 cells at concentrations up to 1 mg/ml. Taurocholic acid administered at 1.9 g/kg to a rabbit of 1.5 kg did not show any toxicity within the 8-h observation period.

2.7. Pharmacokinetic calculations

The concentrations of AMD3100 in serum after intravenous injection or oral dosing in the presence or absence of taurocholic acid were analyzed by using the curve-fitting software package Siphar/win (Simed, Créteil, France). The values for the area under the curve from time zero to infinity ($AUC_{0-t\infty}$) and the area under the first moment curve from time zero to infinity ($AUMC_{0-t\infty}$) were calculated by the linear trapezoidal rule. The bioavailability of AMD3100 following oral administration of AMD3100 in the presence or absence of 4 equivalents of taurocholic acid was defined as $100 \times (AUC_{p.o.,\ 0-t\infty}/AUC_{iv.,\ 0-t\infty}) \times (D_{i.v.}/D_{p.o.})$, where $AUC_{p.o.,\ 0-t\infty}$ equals the AUC for AMD3100 following oral administration of AMD3100 (250 mg) in the presence or absence of 4 equivalents of AMD3100, and $AUC_{i.v.,\ 0\text{-}t\infty}$ equals the AUC for AMD3100 following intravenous injection of AMD3100 (2.5 mg). The mean residence time (MRT) was calculated as $AUMC_{0-t\infty}/AUC_{0-t\infty}$. Maximum concentrations in plasma (C_{max}) and times to C_{max} (T_{max}) were the observed values. The plasma concentration-*versus*-time curves were further analyzed by biexponential equations to determine the terminal elimination rate constant (k_{el}), terminal half-life ($0.693/k_{el}$), and total body clearance.

3. Results and discussion

Ion pairs can be defined as neutral species formed by electrostatic interaction between oppositely charged ions in solution, which are often sufficiently lipophilic to dissolve in non-aqueous solvents (Quintanar-Guerrero et al., 1997). Several studies suggest that the formation of ion pairs could be used for an enhancement in membrane transport of charged molecules (Neubert et al., 1989b; Pardo et al., 1992; Brayden et al., 1997; Meyer and Manning, 1998).

In this study, we evaluated ion pair formation as a strategy to enhance transepithelial transport of two charged antiviral drugs: PMPA and AMD3100 (Fig. 1). Preliminary partitioning experiments performed with both compounds in the presence of their respective counter ions between n-octanol and pure water had shown that ion pair formation is possible (Table 1). For PMPA, two series of counter ions were used: cetrimides with increasing chain lengths (C12, C14, C16) and three different tetra-alkylammonium bromides (C6, C7, C8). Ion pair formation appeared to be dependent on the chain length of the counter ion used, with more PMPA disappearing from the aqueous phase when using counter ions of longer chain length. The n-octanol/water partition coefficient (log P) was reported to be -2.5 (Arimilli et al., 1997), while in the presence of hexadecyltrimethylammonium bromide (5 mM), the log P of PMPA (10 μM) amounted to 0.49 ± 0.03.

An increase in *n*-octanol/water partition coefficient was also observed for AMD3100 (200 μM) in the presence of taurodeoxycholic acid (4 mM). The log P of AMD3100 was -2.80 ± 0.11 in the absence of counter ion, while the presence of taurodeoxycholic acid at a drug/counter ion ratio of 1/20 resulted in a log P value of -0.26 ± 0.04. These data show that for PMPA as well as AMD3100 a lipophilic complex is formed when the counter ions are present in pure water.

To evaluate the effect of ion pair formation on transepithelial transport of PMPA and AMD3100,

Table 1
Partitioning studies with PMPA (10–300 μM) between *n*-octanol and several aqueous phases (water, NaCl, isotonic phosphate buffer) in the presence of different counter ions for the drug[a]

Counter ion	Counter ion concentration (mM)	Concentration of PMPA (μM)	Aqueous phase	% of PMPA remaining in aqueous phase
Reference	/	10	Water	100.2 ± 0.5
t-hexylammonium bromide	1	10		81.5 ± 0.8
	2.5	10		71.0 ± 0.2
	5	10		60.3 ± 0.5
t-heptylammonium bromide	5	10	Water	54.0 ± 6.6
t-octylammonium bromide	5	10	Water	44.7 ± 1.0
Dodecyltrimethylammonium bromide	5	10	Water	66.9 ± 0.3
Tetradecyltrimethylammonium bromide	5	10	Water	42.0 ± 2.1
Hexadecyltrimethylammonium bromide	5	10	Water	24.4 ± 1.4
		100		34.2 ± 0.4
		300		51.1 ± 1.3
		10	NaCl 25 mOsm	98.2 ± 1.1
		10	NaCl 50mOsm	97.0 ± 0.8
		10	Isotonic buffer	104.8 ± 4.6
		100		101.5 ± 3.0
		300		103.4 ± 3.7

[a] Values are expressed as the percentage of drug remaining in the aqueous phase after 1 h partitioning between the two phases (average $\pm$ SD; $n = 3$).

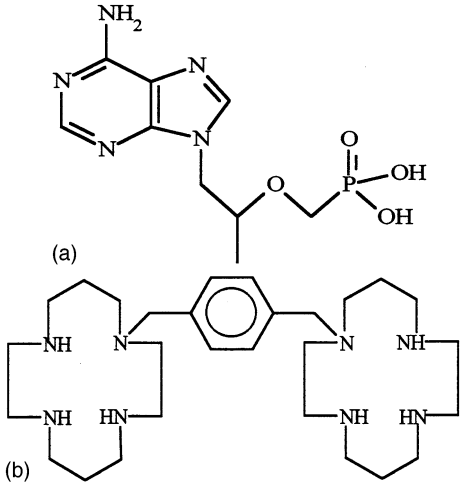

Fig. 1. (a) Structural formula of PMPA. (b) Structural formula of AMD3100.

we studied their flux across Caco-2 monolayers in the absence or presence of counter ions. For this study, hexadecyltrimethylammonium bromide and taurodeoxycholic acid were selected as counter ions for AMD3100 and PMPA, respectively. Initial experiments were conducted at a nominal concentration of 1 mM for both PMPA and AMD3100. Concentrations of counter ion amounted up to 10 mM for hexadecyltrimethylammonium bromide and to 20 mM for taurodeoxycholic acid. In the absence of counter ions, no transport of PMPA or AMD3100 could be observed ($< 0.1\%$ after 2 h) (Fig. 2). A significant ($P < 0.05$) concentration dependent enhancement in transport was observed for PMPA (1 mM) as well as AMD3100 (1 mM) at a high counter ion/drug ratio; however, under these conditions, the monolayer integrity was compromised, which could be concluded from a decrease in TEER values and an increase in flux of the paracellular leakage marker sodium fluorescein (Figs. 3 and 4). To exclude a detrimental effect on the monolayers, similar transport experiments were conducted for AMD3100 at a lower concentration (200 μM), maintaining similar drug/counter ion ratios. The results of this system are shown in Fig. 2b. Under these conditions, the monolayer integrity remained intact ; AMD3100 could not be detected in the basolateral compartment, even at a drug/counter ion ratio of 1/20, which corresponds to a concentration of 4 mM of taurodeoxycholic acid. These results clearly suggest that no absorption enhancing effect can be observed by the addition of low concentrations of counter ions and that the absorption enhancement observed at a high absolute concentration of counter ions is probably due to their effect on cell monolayer integrity. A concentration of 12.5 mM of taurodeoxycholic acid has indeed been reported to have an absorption enhancing effect in vivo

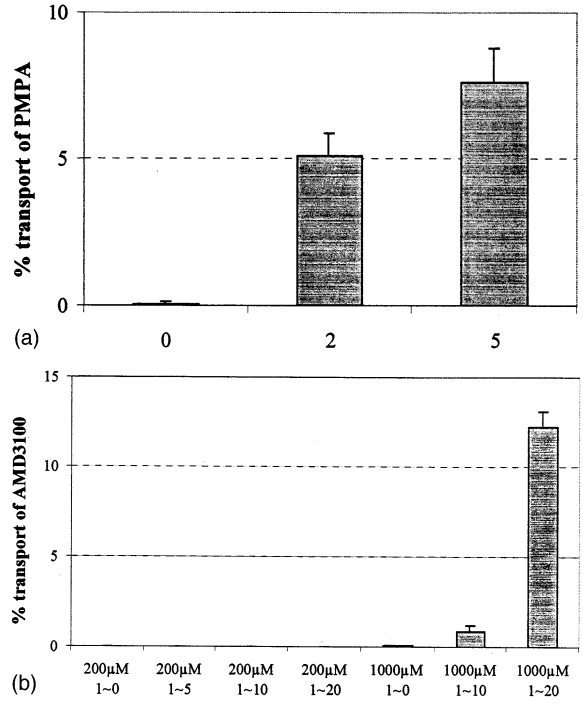

Fig. 2. (a) Transport of PMPA (1 mM) across Caco-2 monolayers for 2 h in the absence or presence of tetrahexyltrimethylammonium bromide (0–5 mM). Transport is expressed as percentage of PMPA in the basolateral compartment of the initial concentration in the donor compartment. The values are the average ± SD; $n = 3$. All groups were significantly different ($P < 0.05$) from each other (two-tailed Student's t-test). (b) Transport of AMD3100 (200 and 1000 μM) across Caco-2 monolayers for 2 h in the presence of taurodeoxycholic acid at different drug/counter ion ratios. Transport is expressed as percentage of AMD3100 in the basolateral compartment of the initial concentration at the donor side. The values are the average ± SD; $n = 3$. All the conditions at a concentration of 1000 μM of AMD3100 were significantly different ($P < 0.05$) from each other (two-tailed Student's t-test).

(Swenson and Curatolo, 1992). TEER values increased when AMD3100 was present in the medium bathing the apical compartment (Fig. 3a); the reason for this increase is still unclear, but might be due to saturation of the paracellular transport of cations (Lee and Thakker, 1998).

To test the potential of ion pair formation in the experimental conditions of the transport study, we performed several additional partitioning studies using various aqueous solutions: pure water, NaCl 25–50 mOsm and TM (pH 7.4, 270–305 mOsm). As discussed earlier, ion pair formation clearly occurred when pure water was used; however, as soon as other ions were present in the aqueous phase, PMPA and AMD3100 remained in the aqueous phase (Table 1 and Fig. 5), which indicates that ion pair formation is dimished or even lost when other ions are present, due to competition between counter ion and other ions present in the medium.

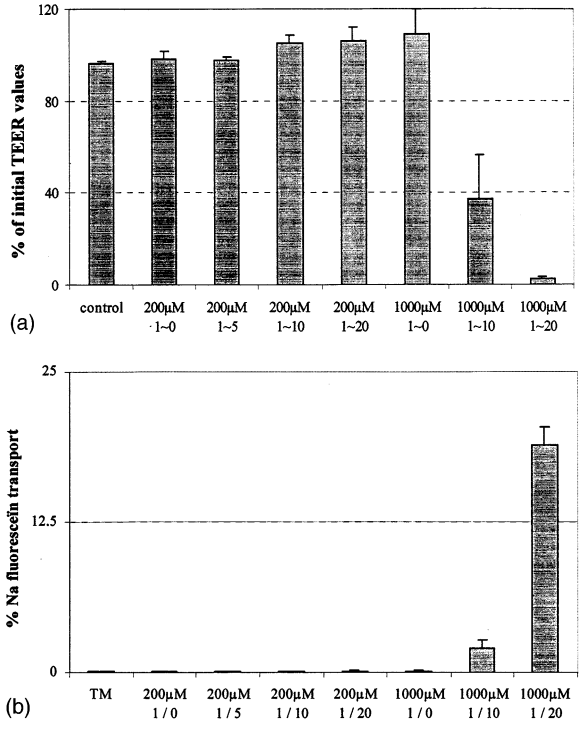

Fig. 3. (a) TEER values observed after transport experiment with AMD3100 (200–1000 μM) in the presence of taurodeoxycholic acid at different drug/counter ion ratios. Values are expressed as the average percentage of the initial TEER values ($n = 3$). (b) Sodium fluorescein transport after 1 h across Caco-2 monolayers, experiment performed as a control for paracellular leakage after transport experiment performed with AMD3100 (200–1000 μM) in the presence of taurodeoxycholic acid at different drug/counter ion ratios. Values are expressed as percentages of sodium fluorescein in the receptor compartment of the initial concentration at the donor side. The values are the average ± SD; $n = 3$.

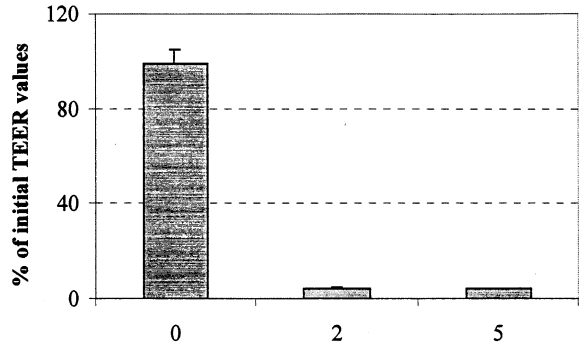

Fig. 4. TEER values after transport experiment of PMPA (1 mM) in the presence of tetrahexyltrimethylammonium bromide at different concentrations (0–5 mM). Values are expressed as percentages of the initial TEER values. The values are the average ± SD; $n = 3$.

In addition to the in vitro transport experiments and the partitioning studies, the influence of counter ions on the in vivo oral bioavailability of AMD3100 was evaluated in rabbits. The drug concentration-*versus*-time curve after the intravenous bolus injection of AMD3100 in rabbits showed a rapid and biphasic decline (Fig. 6), with a terminal half-life of 105 min (Table 2). Oral administration of pure AMD3100 at a dose of 250 mg/kg resulted in serum concentrations of maximum 3.1 μg/ml, and a bioavailability (using the AUC values from 0 to infinity) of only 1.1%. Only 2.5-fold higher C_{max} values of AMD3100 were obtained in serum upon oral administration of AMD3100 + 4 equivalents of taurocholic acid (Fig. 6). In rabbits receiving AMD3100 + 4 equivalents of taurocholic acid at an oral dose of 250 mg of AMD3100 per kg, the C_{max} of AMD3100 was 7.8 μg/ml, with a T_{max} of 83 min. The oral bioavailability was 3.6% (Table 2). On the basis of the first-moment analysis of the drug concentration-*versus*-time curves, MRTs for intravenous AMD3100 and oral AMD3100 + 4 equivalents of taurocholic acid were calculated to be 2.2 and 3.3

Table 2
Pharmacokinetic parameters in rabbits for intravenous AMD3100 or oral AMD3100 in the presence or absence of 4 equivalents of taurocholic acid (mean values)[a]

Compound and route of administration	Dose (mg/kg)	Terminal half-life (h)	Total body clearance (l kg^{-1} h^{-1})	C_{max} in serum (μg/ml)	T_{max} in serum (h)	$AUC_{0\text{-}t\infty}$ (μg h ml^{-1})	$AUMC_{0\text{-}t\infty}$ (μg h^2 ml^{-1})	MRT (h)	Oral bioavailability (%)
AMD3100, i.v. ($n=1$)	2.50	1.74	0.38	—	—	6.53	14.40	2.20	—
AMD3100, p.o.($n=2$)	250	1.37	0.38	3.07	0.88	7.47	20.21	2.60	1.14
AMD3100+4 equivalents of tauro-cholic acid, p.o. ($n=4$)	250	2.36	0.38	7.81	1.38	23.74	80.73	3.28	3.63

[a] Pharmacokinetic parameters were calculated by the method described in the Section 2. i.v., intravenous; p.o., per os.

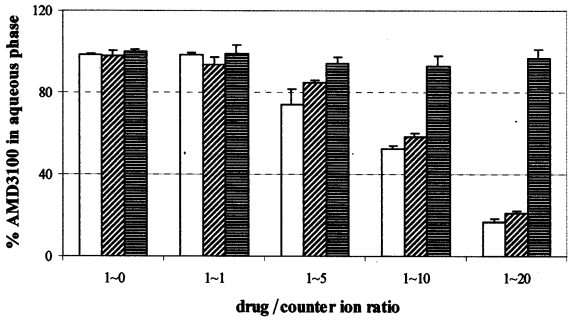

Fig. 5. Partitioning studies with AMD3100 (200 μM) between *n*-octanol and several aqueous phases [water (open bars), NaCl 50 mOsm (diagonal bars), TM (horizontal bars)] in the presence of taurodeoxycholic acid as a counter ion for the drug at different drug ~ counter ion ratios. Values are expressed as the percentage of drug remaining in the aqueous phase after 1 h partitioning between the two phases. The values are the average ± SD; $n = 3$.

h, respectively (Table 2), thus yielding a mean absorption time of 1.1 h for the appearance of AMD3100 in serum after the oral administration of AMD3100 + 4 equivalents of taurocholic acid. Altough the inclusion of 4 equivalents of taurocholic acid resulted in a statistically significant higher bioavailability ($P < 0.05$ by two-tailed Student's *t*-test), this effect could hardly be considered as clinically useful, as the absolute oral bioavailability (3.6%) remained far under an acceptable level. In view of the results with the Caco-2 model, the increase in oral bioavailability of AMD3100 is probably due to the effect of taurocholic acid on the integrity of the monolayer.

In conclusion, the results of this study suggest that the use of counter ions with two charged antiviral drugs, AMD3100 and PMPA, may be inefficient as a strategy to enhance the transepithelial transport of charged hydrophilic compounds, as competition by other ions probably abolishes the beneficial effect of counter ions. As has been demonstrated for PMPA (i.e. bis(POC)-PMPA), a lipophilic prodrug for AMD3100 should be considered as a more efficient avenue to increase its absorption after oral administration.

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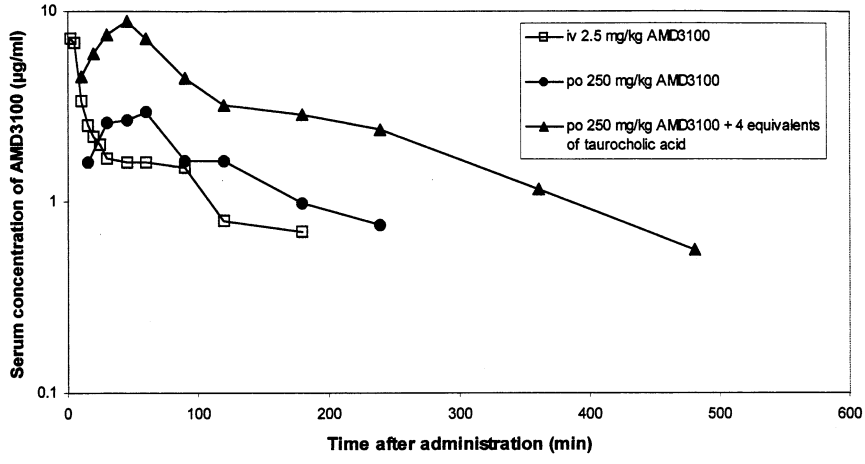

Fig. 6. Profiles of the concentration of AMD3100 in the serum of rabbits after intravenous bolus injection of 2.5 mg/kg of AMD3100 (□) or oral gavage of 250 mg/kg AMD3100 (●) or 250 mg/kg AMD3100 + 4 equivalents of taurocholic acid (▲). Data are the average values of at least two independent experiments.

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