Rapport de synthèse

UNIVERSITE DE LAUSANNE – FACULTE DE BIOLOGIE ET DE MEDECINE

Département de Médecine

Division Spécialisée de Pharmacologie et Toxicologie Cliniques

Effect of dronedarone on renal function in healthy subjects

THESE

préparée sous la direction du Professeur Jérôme Biollaz, médecin chef de la Division Spécialisée de Pharmacologie et Toxicologie Cliniques au CHUV,

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Yvonne TSCHUPPERT

Médecin diplômée de la Confédération Suisse

Originaire de Grosswangen (LU)

Lausanne

2008

Rapport de synthèse

Effet de la dronédarone sur la fonction rénale de volontaires sains masculins

But

Evaluer l'effet de la dronédarone sur la fonction rénale et le transport tubulaire des cations.

Méthodes

Douze sujets masculins en bonne santé ont été inclus dans une étude randomisée, croisée, comparée à un placebo, en double aveugle. Ils ont reçu 400 mg de dronédarone ou un placebo deux fois par jour pendant sept jours. Des tests fonctionnels rénaux ont été effectués avant le traitement et en cours de traitement après une standardisation stricte des apports, par détermination de la clairance de la créatinine, de la sinistrine, du para-amino-hippurate (PAH) et du N-méthylnicotinamide (NMN) et de l'excrétion des électrolytes.

Résultats

Comparée au placebo, la dronédarone a réduit de manière significative la clairance de la créatinine (en moyenne 138-119 ml/min après dronédarone vs 142-149 ml/min après placebo) et la clairance du NMN (448-368 ml/min vs 435-430 ml/min), mais n'a pas eu d'effet sur la clairance rénale de la sinistrine, du PAH ou sur d'autres paramètres rénaux.

Conclusion

La dronédarone réduit la clairance rénale de la créatinine et du NMN d'environ 18%, sans évidence d'effet sur la filtration glomérulaire, sur le flux plasmatique rénal ou sur les échanges électrolytiques. Cela suggère une inhibition spécifique partielle du transport tubulaire organique des cations (OCT). Une augmentation limitée de la créatininémie est donc à attendre sous traitement de dronédarone, sans que cela ne soit assimilable à une baisse de la fonction rénale.

DOI:10.1111/j.1365-2125.2007.02998.x

Effect of dronedarone on renal function in healthy subjects

Yvonne Tschuppert,[1] Thierry Buclin,[1] Laura E. Rothuizen,[1] Laurent A. Decosterd,[1] Jacques Galleyrand,[2] Christine Gaud[2] & Jérôme Biollaz[1]

[1]*Clinical Pharmacology and Toxicology, University Hospital, Lausanne, Switzerland and* [2]*Sanofi-Aventis, Montpellier, France*

What is already known about this subject

- Creatinine clearance (CL) is used to assess glomerular filtration rate (GFR). However, it is known to slightly overestimate the true GFR, due to renal tubular secretion of creatinine.
- During phase I-III clinical trials, a 10–15% increase in serum creatinine has been observed both in healthy subjects and patients receiving the new antiarrhythmic agent dronedarone.

What this study adds

- Dronedarone affects the renal handling of creatinine and N-methylnicotinamide, two cations, while leaving unchanged GFR, assessed through sinistrin CL, and renal plasma flow and anion secretion, assessed through para-amino-hippurate CL.
- This suggests a specific action of dronedarone on renal organic cation transport explaining the limited, reversible effect of dronedarone on serum creatinine, which must not be interpreted as reflecting an impairment of renal function, but which may indicate an interaction potential with cationic drugs.

Correspondence
Dr T. Buclin, Division of Clinical Pharmacology and Toxicology, Beaumont 633, University Hospital of Lausanne (CHUV), 1011 Lausanne, Switzerland.
Tel.: +41 2 1314 4260
Fax: + 41 2 1314 4266
E-mail: thierry.buclin@chuv.ch

Keywords
creatinine clearance, dronedarone, organic cation transport

Received
9 March 2007
Accepted
11 May 2007

Aims
To assess the effects of dronedarone on renal function and tubular cation handling.

Methods
Twelve healthy males were enrolled in a randomized, cross-over, placebo-controlled, double-blind study. They received 400 mg dronedarone or placebo twice daily for 7 days. Baseline and on-treatment renal function tests were performed under strict standardization of intakes, by assessing creatinine, sinistrin, para-amino-hippurate (PAH) and N-methylnicotinamide (NMN) CLs, and electrolyte excretion.

Results
Compared with placebo, dronedarone significantly decreased renal creatinine CL (mean 138–119 ml min^{-1} after dronedarone *vs.* 142–149 ml min^{-1} after placebo) and NMN CL (448–368 ml min^{-1} *vs.* 435–430 ml min^{-1}), but did not alter renal sinistrin CL, PAH CL and other renal parameters.

Conclusions
Dronedarone reduces renal creatinine and NMN clearance by about 18%, without evidence of an effect on GFR, renal plasma flow or electrolyte exchanges. This suggests a specific partial inhibition of tubular organic cation transporters (OCT). A limited increase in serum creatinine is therefore expected with dronedarone treatment, but does not mean there is a decline in renal function.

Introduction

Creatinine, an endogenous cation produced mainly by muscle metabolism, is the most widely used marker to assess glomerular filtration rate (GFR) in the clinical setting. However, creatinine clearance is known to slightly overestimate the true GFR, as it is secreted up to 20% across the renal tubule through an active cationic transport, in addition to the amount filtered at the glomerulus [1]. Several drugs, such as cimetidine and trimethoprim [2, 3], are known to interfere with creatinine transport across tubular epithelial cells. Such drugs inhibit the organic cation transport system located in the renal proximal tubule, thus decreasing creatinine clearance (CL_{Cr}) and increasing serum creatinine concentration without altering the GFR itself. This effect of cimetidine has been used in clinical practice to improve the accuracy of CL_{Cr} measurement as an estimation of GFR [4].

Dronedarone is a noniodinated benzofuran derivative with pharmacological activity similar to amiodarone [5–7], to which it is structurally related, and shares electrophysiological characteristics of all four Vaughan-Williams classes of antiarrhythmics [8–10]. It is less likely to induce the thyroid adverse events observed with amiodarone. Targeted indications are atrial fibrillation and flutter. During phase I-III clinical trials, a 10–15% increase in serum creatinine has been regularly observed both in healthy subjects and patients receiving dronedarone, without any clinical or laboratory evidence of renal structural damage. This effect seemed to be rapid and reversible, with a quick return to baseline values occurring after study drug discontinuation. In animal studies, no histological changes were noted in the kidneys despite a slight increase in serum creatinine concentrations (5–15%) [11]. An artefactual interference with creatinine measurement methods (e.g. Jaffé method) was excluded.

Carrier-mediated transporters play an important role in renal tubular reabsorption and secretion of a number of endogenous and exogenous compounds [12]. A majority of transporters represent oligospecific carrier proteins involved in the transfer of specific metabolic and nutritional compounds (SLC19 transporter family). By contrast, drugs and toxins are transferred by a limited number of polyspecific transporters accepting compounds of variable size and molecular structure. In addition to the ATP-binding-cassette family (including P-glycoprotein and related proteins), three families of ATP-independent polyspecific transporters have been identified to date: the H^+-oligopeptide cotransporter family SLC15 (solute carrier family 15), the solute carrier organic anion transporter family SLCO (SLC21) and the organic cation-anion-zwitterion transporter family SLC22. The latter includes three organic cation transporters (OCT1-3), four organic anion transporters (OAT1-4), one urate transporter, three transporters of carnitine and/or cations (OCTN1,2 and CT2) and six gene products of unidentified function [13]. The distribution of these various carrier subtypes throughout the body is not completely elucidated. However, most subtypes are expressed in the kidney, consistent with its elimination function, with the main subtype being probably OCT2 [14–16]. The transporters involved in renal tubular secretion contribute to the elimination of organic compounds that are weakly filtrated, owing to strong protein binding. Transporters are also found in other organs involved in the defence against toxins, such as the liver, the intestine and the placenta [17], and this mechanism is saturable [18].

Creatinine, a zwitterion, is secreted to a moderate extent by the renal tubular cation transport system and minimally by anion transporters [19]. It has low affinity for OCT2, with a Michaelis constant of 4000 $\mu mol\ l^{-1}$, and its renal transport is readily inhibited by various drugs [12]. As a cation, dronedarone, though mainly eliminated through biliary excretion, may compete for the cation transport pathway and thus inhibit creatinine secretion in a cimetidine-like way, thereby leading to a limited increase in serum creatinine concentrations. Considering the use of creatinine clearance or serum creatinine concentration to assess renal function, it appeared suitable to confirm the hypothesis of an interference of dronedarone with such tests, while excluding a direct action of this new drug on GFR or renal integrity.

To investigate GFR independently of cation transport, sinistrin, an inulin-like polyfructosan with high solubility, represents an ideal marker as it is almost exclusively eliminated by filtration [1, 20]. N-methylnicotinamide (NMN), produced during tryptophan and niacin metabolism, is an endogenous substrate of the active cation secretion system, and the assessment of its clearance has been proposed to test the organic cation secretion and the renal plasma flow [21–23]. On the other hand, para-amino-hippurate (PAH) is used to study the active anionic secretion; as it is highly extracted, PAH has also been established as the standard marker for determination of the renal plasma flow [1].

The aim of this phase I study was thus to evaluate the effects of dronedarone, compared with placebo, on creatinine clearance and on glomerular filtration rate assessed by renal sinistrin clearance, in healthy subjects. Secondary objectives were to evaluate the effects of dronedarone on two markers of tubular transport and

renal blood flow, one exogenous substrate of the anionic transport system (PAH) and one endogenous substrate of the cationic transport system (NMN).

Methods

Subjects

Twelve healthy male subjects with mean age of 26 years (range 19–38 years), mean weight of 68 kg (range 56–88 kg), mean height of 179 cm (range 169–192 cm) and mean body mass index (BMI) of 21 kg m^{-2} (range 19–24.6 kg m^{-2}) gave their written informed consent before initiation of the study, after the protocol had been approved by the Research Ethics Committee of the University Hospital of Lausanne, Switzerland. All subjects were considered healthy after detailed medical history, physical examination (including a 12-lead electrocardiogram, echocardiography and a 24 h Holter recording) and extensive laboratory tests (haematology, biochemistry, serology and urinalysis). No medication was allowed within 2 weeks prior to dronedarone administration and throughout the duration of the study, except the use of acetaminophen in case of pain.

Drugs

Dronedarone 400 mg tablets were supplied by Sanofi-Aventis (Montpellier, France). For determination of the sinistrin clearance, Inutest® vials of 5 g 20 ml^{-1} were purchased from Fresenius Kabi Austria GmbH (Graz, Austria). Sodium para-amino-hippurate (PAH) vials of 2 g 10 ml^{-1} were obtained from Clinalfa, Merck Biosciences AG (Läufelfingen, Switzerland).

Study design and procedures

This was a monocentre, randomized, placebo-controlled, double-blind cross-over study. It consisted of two periods during which each subject received twice daily repeated doses of either 400 mg dronedarone or placebo for 7 days, separated by a 14 day washout period. The subjects underwent renal investigations on five occasions: on the day before treatment (day −1) and on the last day of treatment (day 7) of each period, then 14 days after the last study drug administration. From the day before each renal investigation, subjects were on a diet with strict standardization of food and liquid intakes. A 24 h urine collection was obtained for measurement of creatinine, osmolality, sodium and potassium excretion on day −1. For the investigation, an intravenous catheter was inserted in each forearm (Optiva; Johnson & Johnson Medical, Arlington, TX), one for sinistrin and PAH infusion and one for blood sampling. Subjects received a standardized breakfast, followed by the study drug with 200 ml water. Sinistrin and PAH infusion started 0.5 h after treatment administration (or corresponding time on the days without treatment). A loading dose of 18.75 mg $kg^{-1}{}_{IBW}$ sinistrin and 3.6 mg $kg^{-1}{}_{IBW}$ PAH was administered over 3 min to achieve quickly a pseudo-steady-state plasma concentration of 75 mg l^{-1} for sinistrin and 12 mg l^{-1} for PAH. Immediately thereafter, a maintenance infusion designed to bring 9 mg h^{-1} of sinistrin and 7.2 mg h^{-1} of PAH per ml min^{-1} GFR (estimated from serum creatinine by the Cockroft-Gault formula) was started and maintained during 6 h, using a high-precision pump (Pilote C; Fresenius Vial, Brezins, France). Blood samples for measurement of plasma creatinine, sinistrin, PAH and NMN were collected before and at 2, 3.5, 5 and 6.5 h after drug administration. The samples were centrifuged and plasma was separated and stored at −20°C until analysis. The haematocrit of each sample was also assessed. Urine was collected from 2 to 3.5, 3.5–5 and 5–6.5 h for creatinine, sinistrin, PAH and NMN measurements, the volume determined and an aliquot stored at −20°C. A fixed amount of water (6 × 200 ml) was given for hydration during the investigation day. Before and after the treatment period, haematology and biochemistry tests were repeated for safety assessment.

No medication, xanthine containing drinks (coffee, tea, coke) or alcohol were allowed during the investigation and treatment periods. Smoking and strenuous sport were prohibited during the entire study period.

Analytical methods

Plasma and urine concentrations of sinistrin, PAH and NMN were determined by validated high-performance liquid chromatography (HPLC) methods with electrochemical detection (limit of detection 0.8 μg ml^{-1}, precision between 6.3 and 9.7% in plasma and 4.2–10.2% in urine) and UV detection (limit of detection in plasma 0.2 μg ml^{-1}, precision between 3.3 and 4.4% in plasma, 2.0–2.8% in urine) and after derivatization and using fluorescence detection (limit of detection 0.25 ng ml^{-1} in plasma, 8 ng ml^{-1} in urine, precision between 1.1 and 3.3% in plasma and 5.6–8.3% in urine), respectively [24–26]. Creatinine was measured by the standard Jaffé colorimetric method.

Data analysis

Creatinine, sinistrin, PAH and NMN renal clearances were calculated from the three urine collections (concentration = U, volume = V, duration = Δt) and from the geometric mean of the blood concentrations measured at each start and end of collection periods (concentration = P), using the following standard formula:

$$CL_R = (U \times V)/(P \times \Delta t)\ [27]$$

Knowing the infusion rate (R) of sinistrin and PAH, determined by careful assessment of the marker concentration in the solution and of the flow rate of the pump [28], enabled the calculation of their respective systemic clearance: $CL_S = R/P$. Systemic clearance calculated this way has more inertia than renal clearance to reflect sudden and short-term changes in kidney function [27]. For creatinine and NMN, systemic clearance was estimated in a similar way, assuming a constant production rate (R) which was estimated for each subject as his average excretion rate throughout the study.

Renal sinistrin clearance was considered the reference value for determination of the glomerular filtration rate. Renal blood flow was calculated from the renal and systemic PAH clearances and from the haematocrit: $RBF = CL_{PAH}/(1 - Ht)$. Renal creatinine clearance was also determined from the 24 h urine collection, which also allowed the measurement of excreted amounts of sodium, potassium and water.

Statistical analysis

Statistical analysis was performed using a linear mixed effect model with fixed terms and a random term for subjects within sequence. The relative changes of clearances from baseline to the 7th day of treatment were expressed in percent, based on means of log-transformed values and compared between dronedarone and placebo using ANOVA, which accounted for subject, sequence, period and time effects.

Results

Subjects

Twenty subjects had to be screened to obtain 12 healthy male subjects for inclusion in the study protocol (five subjects were excluded because of benign arrhythmia in 24 h Holter examination, and three declined for personal or convenience reasons). All enrolled subjects completed the study.

Renal function tests

Results are presented in Table 1 and Figure 1. No differences in the various clearances could be noted between the treatment periods at baseline. After 7 days of treatment, dronedarone significantly affected renal creatinine clearance, which decreased by 17.7% (95% CI −31.7, −0.9) compared with placebo. Sinistrin clearance remained unaffected by dronedarone compared with placebo, with a variation of 3.4% (95% CI −20.4, 17.2). Renal clearance of NMN decreased by 17.0% (95% CI −31.58, 0.65) compared with placebo. Conversely, renal PAH clearance was not affected by dronedarone, with a variation of 5.8% (95% CI −22.5, 14.5). The comparison of systemic clearance values indicated essentially similar changes (not shown). The ratio between renal creatinine and renal sinistrin clearances decreased after 7 days of dronedarone treatment to an average of 1.2, while it remained unchanged at 1.4 after placebo. Similarly, the ratio of renal NMN over renal PAH clearances decreased from 0.9 to 0.8 after dronedarone.

No changes in urine flow rate, osmolality, sodium and potassium excretions were observed between baseline and day 7 of dronedarone treatment compared with placebo.

Safety

No serious adverse event occurred during the study. Nine subjects on dronedarone, and four on placebo presented with treatment-emergent adverse events: one loose stool, two cases of fatigue, one injury, two cases of

Table 1
Geometric means (coefficient of variation, %) of renal and systemic clearances according to treatment and study day

Study variables	Placebo		Dronedarone		*P* value
	Day −1	Day 7	Day −1	Day 7	
CL_R Sin (ml min^{-1})	106 (24%)	107 (19%)	101 (36%)	98 (60%)	NS
CL_R Cr (ml min^{-1})	142 (15%)	149 (12%)	138 (34%)	119 (59%)	0.04
CL_R PAH (ml min^{-1})	514 (24%)	513 (14%)	515 (38%)	486 (66%)	N.S.
CL_R NMN (ml min^{-1})	435 (25%)	430 (20%)	448 (39%)	368 (70%)	0.06
CL_R Cr : CL_R Sin	1.34 (17%)	1.39 (15%)	1.37 (19%)	1.21 (12%)	0.0001
CL_R NMN : CL_R PAH	0.85 (25%)	0.84 (20%)	0.87 (20%)	0.76 (35%)	0.007

CL_R renal clearance; Sin, sinistrin; Cr, creatinine; PAH, para-amino-hippurate; NMN, N-methylnicotinamide; CL_R Cr : CL_R Sin, ratio of renal clearances of creatinine over sinistrin; CL_R NMN : CL_R PAH, ratio of renal clearances of N-methylnicotinamide over para-amino-hippurate. NS: non significant

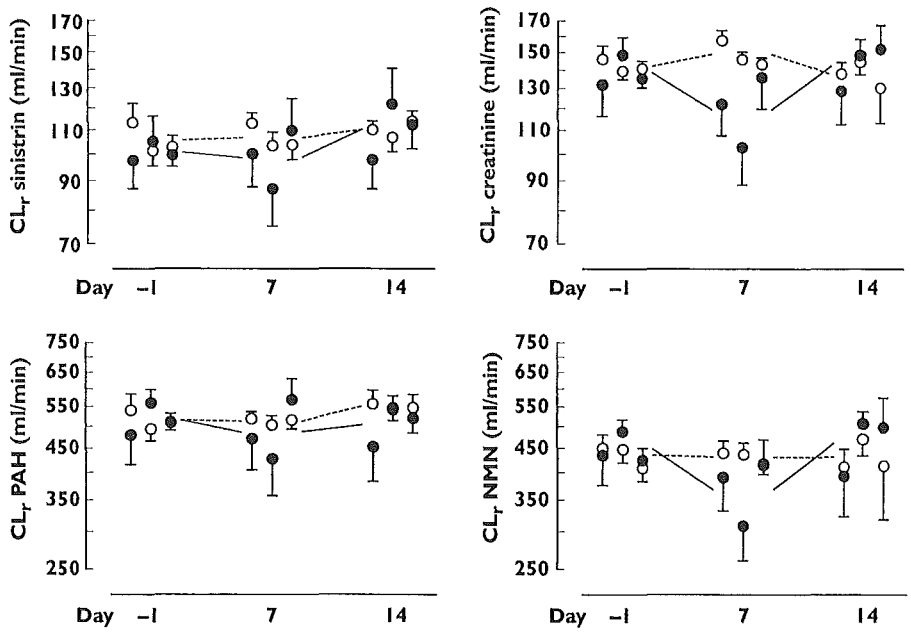

Figure 1
Mean renal clearances (SD) of creatinine, sinistrin, NMN and PAH in 12 healthy subjects after twice daily repeated doses of either 400 mg dronedarone (●) or placebo (○) (geometric average with coefficient of variation). For clarification only one side SD is represented

back pain, one musculoskeletal pain, one dizziness, five cases of headache, two cases of nasal congestion and one erythema after dronedarone treatment; one dyspepsia, one back pain, one myalgia and two cases of headache after placebo treatment. No clinically relevant changes were observed in the laboratory tests.

Discussion

The results of this study indicate that dronedarone has no influence on renal clearance of sinistrin, and therefore does not affect the glomerular filtration rate in the study subjects. By contrast, dronedarone significantly decreases renal creatinine clearance by about 18%. This observation is consistent with an inhibition of the cationic transport system by this antiarrhythmic drug, in a way similar to cimetidine. Interestingly, a similar effect has been confirmed for amiodarone during long-term therapy [29].

A significant and similar decrease was observed in the renal clearance of another cation, NMN. Renal clearance of the anion PAH was not affected. This tends to confirm an inhibitory action of dronedarone specifically on the tubular cation transport system. The carriers involved in drug transportation being polyspecific, dronedarone could have a higher affinity than other drugs eliminated in this way, thus leading to their decreased clearance. The fact that PAH clearance remained stable indicates that renal plasma flow was not affected by dronedarone. NMN has also been proposed as an endogenous marker for the determination of renal blood flow [1, 26, 30]. This study indicates however, that it is less efficiently removed from renal blood than PAH, as its clearance is 20% to 30% lower. Moreover, NMN may be affected by inhibitors of cationic transport, but similarly PAH is known to be influenced by anion transporter inhibitors [31–33]. Other variables of renal physiology like diuresis, renal filtration fraction, urinary sodium and potassium excretion and osmolality, measured under strict standardization of food and fluid intake, remained unaffected after 7 days of dronedarone treatment, which suggests an absence of any other renal effects of this drug.

Creatinine clearance impairment by dronedarone, though compatible with an inhibition of the OCT system, was lower than expected. Had tubular creatinine secretion been completely blocked by dronedarone, the ratio between renal creatinine and renal sinistrin clearances would have reached 1.0, as observed with cimetidine for example. In fact, the observed ratio decreased only to 1.2, while it remained at 1.4 on placebo, meaning a partial inhibition of the tubular creatinine secretion. This could be related either to an inhibition by dronedarone of only certain subclasses of the OCT system, while creatinine may be secreted by other transporters, including OATs, or to incomplete inhibition of creatinine transport at the dose administered. Further studies are warranted to investigate the dose-dependency of this interference of dronedarone on the renal handling of creatinine. It would be of interest to determine whether the drug has any effect on creatinine clearance after full inhibition of tubular secretion by cimetidine, or whether it affects Cystatin C plasma concentrations. It would also be important to assess the effect of dronedarone on

other cationic drugs undergoing tubular secretion as a major route of elimination. Such a mechanism of drug interactions affecting cationic transport has been shown, for example, for amantadine (interaction with quinine and quinidine) [24, 34], metformin (interaction with cimetidine) [35] and procainamide (inhibited by trimethoprim) [36], and may induce adverse events.

In conclusion, our results show that dronedarone reduces renal creatinine clearance by about 18% in healthy subjects, without affecting GFR, as confirmed by unchanged sinistrin clearance. This new antiarrhythmic agent is thought to inhibit partially the renal cation transport system involved in creatinine and NMN secretion, like cimetidine, trimethoprim or amiodarone, and does not seem to have other effects on renal physiology. This suggests a potential for drug interactions involving cationic drugs. Dronedarone may induce a limited increase in serum creatinine, which is not correlated to a decline in renal function.

We would like to thank Monique Appenzeller, Monique Salvi, Ali Maghraoui, Philippe Rousso and Yannick Perrin for their valuable contribution to this work. The sponsor of the study was Sanofi-Aventis.

References

1 Tett SE, Kirkpatrick CM, Gross AS, McLachlan AJ. Principles and clinical application of assessing alterations in renal elimination pathways. Clin Pharmacokinet 2003; 42: 1193–211.

2 Andreev E, Koopman M, Arisz L. A rise in plasma creatinine that is not a sign of renal failure: which drugs can be responsible? J Intern Med 1999; 246: 247–52.

3 Burgess E, Blair A, Krichman K, Cutler RE. Inhibition of renal creatinine secretion by cimetidine in humans. Ren Physiol 1982; 5: 27–30.

4 Kemperman FA, Surachno J, Krediet RT, Arisz L. Cimetidine improves prediction of the glomerular filtration rate by the Cockcroft-Gault formula in renal transplant recipients. Transplantation 2002; 73: 770–4.

5 Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. Eur Heart J 2003; 24: 1481–7.

6 Damy T, Pousset F, Caplain H, Hulot JS, Lechat P. Pharmacokinetic and pharmacodynamic interactions between metoprolol and dronedarone in extensive and poor CYP2D6 metabolizers healthy subjects. Fundam Clin Pharmacol 2004; 18: 113–23.

7 Kathofer S, Thomas D, Karle CA. The novel antiarrhythmic drug dronedarone: comparison with amiodarone. Cardiovasc Drug Rev 2005; 23: 217–30.

8 Sun W, Sarma JS, Singh BN. Chronic and acute effects of dronedarone on the action potential of rabbit atrial muscle preparations: comparison with amiodarone. J Cardiovasc Pharmacol 2002; 39: 677–8.

9 Hodeige D, Heyndrickx JP, Chatelain P, Manning A. SR 33589, a new amiodarone-like antiarrhythmic agent: anti-adrenoceptor activity in anaesthetized and conscious dogs. Eur J Pharmacol 1995; 279: 25–32.

10 Gautier P, Guillemare E, Marion A, Bertrand JP, Tourneur Y, Nisato D. Electrophysiologic characterization of dronedarone in guinea pig ventricular cells. J Cardiovasc Pharmacol 2003; 41: 191–202.

11 Data on file, Sanofi-Aventis, Montpellier, France.

12 Dantzler WH. Regulation of renal proximal and distal tubule transport: sodium, chloride and organic anions. Comp Biochem Physiol Mol Integr Physiol 2003; 136: 453–78.

13 Koepsell H. Polyspecific organic cation transporters: their functions and interactions with drugs. Trends Pharmacol Sci 2004; 25: 375–81.

14 Dresser MJ, Leabman MK, Giacomini KM. Transporters involved in the elimination of drugs in the kidney: organic anion transporters and organic cation transporters. J Pharm Sci 2001; 90: 397–421.

15 Urakami Y, Kimura N, Okuda M, Inui K. Creatinine transport by basolateral organic cation transporter hOCT2 in the human kidney. Pharm Res 2004; 21: 976–81.

16 Fujita T, Urban TJ, Leabman MK, Fujita K, Giacomini KM. Transport of drugs in the kidney by the human organic cation transporter, OCT2 and its genetic variants. J Pharm Sci 2006; 95: 25–36.

17 Kusuhara H, Sugiyama Y. Role of transporters in the tissue-selective distribution and elimination of drugs: transporters in the liver, small intestine, brain and kidney. J Control Release 2002; 78: 43–54.

18 Pritchard JB, Miller DS. Mechanisms mediating renal secretion of organic anions and cations. Physiol Rev 1993; 73: 765–96.

19 Sica DA, Schoolwerth AC. Renal handling of organic anions and cations: Excretion of uric acid. In: The Kidney, Brenner BM, ed. Philadelphia: D. Saunders, 2004.

20 Buclin T, Sechaud R, Bertschi AP, Decosterd LA, Belaz N, Appenzeller M, Burnier M, Biollaz J. Estimation of glomerular filtration rate by sinistrin clearance using various approaches. Ren Fail 1998; 20: 267–76.

21 Orlando R, Floreani M, Napoli E, Padrini R, Palatini P. Renal clearance of N(1)-methylnicotinamide: a sensitive marker of the severity of liver dysfunction in cirrhosis. Nephron 2000; 84: 32–9.

22 Maiza A, Daley-Yates PT. Prediction of the renal clearance of cimetidine using endogenous N-1-methylnicotinamide. J Pharmacokinet Biopharm 1991; 19: 175–88.

23 Maiza A, Waldek S, Ballardie FW, Daley-Yates PT. Estimation of renal tubular secretion in man, in health and disease, using endogenous N-1-methylnicotinamide. Nephron 1992; 60: 12–6.

24 Sechaud R, Decosterd LA, Pechere-Bertschi A, Biollaz J,

Kesselring UW. Determination of the polyfructosan sinistrin in biological fluids by HPLC with electrochemical detection. J Pharm Biomed Anal 1996; 14: 483–90.

25 Decosterd LA, Karagiannis A, Roulet JM, Belaz N, Appenzeller M, Buclin T, Vogel P, Biollaz J. High-performance liquid chromatography of the renal blood flow marker p-aminohippuric acid (PAH) and its metabolite N-acetyl PAH improves PAH clearance measurements. J Chromatogr B Biomed Sci Appl 1997; 703: 25–36.

26 Musfeld C, Biollaz J, Belaz N, Kesselring UW, Decosterd LA. Validation of an HPLC method for the determination of urinary and plasma levels of N1-methylnicotinamide, an endogenous marker of renal cationic transport and plasma flow. J Pharm Biomed Anal 2001; 24: 391–404.

27 Buclin T, Pechere-Bertschi A, Sechaud R, Decosterd LA, Munafo A, Burnier M, Biollaz J. Sinistrin clearance for determination of glomerular filtration rate: a reappraisal of various approaches using a new analytical method. J Clin Pharmacol 1997; 37: 679–92.

28 Buclin T, Perrottet N, Biollaz J. The importance of assessing the dose actually administered in pharmacokinetic trials. Clin Pharmacol Ther 2005; 77: 235–40.

29 Pollak P, Alsohaibani F. Changes in serum urea and creatinine during long-term therapy with amiodarone. Clin Pharmacol Ther 2004; 75: P5.

30 Brater DC. Measurement of renal function during drug development. Br J Clin Pharmacol 2002; 54: 87–95.

31 Berkhin EB, Humphreys MH. Regulation of renal tubular secretion of organic compounds. Kidney Int 2001; 59: 17–30.

32 You G. Structure, function, and regulation of renal organic anion transporters. Med Res Rev 2002; 22: 602–16.

33 Lee W, Kim RB. Transporters and renal drug elimination. Annu Rev Pharmacol Toxicol 2004; 44: 137–66.

34 Gaudry SE, Sitar DS, Smyth DD, McKenzie JK, Aoki FY. Gender and age as factors in the inhibition of renal clearance of amantadine by quinine and quinidine. Clin Pharmacol Ther 1993; 54: 23–7.

35 Somogyi A, Stockley C, Keal J, Rolan P, Bochner F. Reduction of metformin renal tubular secretion by cimetidine in man. Br J Clin Pharmacol 1987; 23: 545–51.

36 Vlasses PH, Kosoglou T, Chase SL, Greenspon AJ, Lottes S, Andress E, Ferguson RK, Rocci ML Jr. Trimethoprim inhibition of the renal clearance of procainamide and N-acetylprocainamide. Arch Intern Med 1989; 149: 1350–3.