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Sodium and fluid excretion with torsemide in healthy subjects is limited by the short duration of diuretic action

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ABSTRACT

Background: Loop diuretics are highly natriuretic but their short duration of action permits post-diuretic sodium retention, which limits salt loss unless dietary salt is severely restricted.
We tested the hypothesis that a more prolonged duration of action would enhance salt loss.

Methods and Results: Ten healthy subjects were crossed over between 20 mg of oral immediate release (IR) or extended release (ER) torsemide while consuming a fixed diet with 300 mmol·day^{-1} of Na^+. Compared to IR, plasma torsemide after ER was 59% lower at 1-3 hours, but 97% higher at 8-10 hours due to a >3-fold prolongation of time to maximal plasma concentrations. The relationship of natriuresis to log torsemide excretion showed marked hysteresis but subjects spent twice as long with effective concentrations of torsemide after ER, thereby enhancing diuretic efficiency. Compared to IR, ER torsemide did not reduce creatinine clearance and increased fluid (1634 ± 385 versus 728 ± 445 mL; $p < 0.02$) and Na^+ output (98 ± 15 versus 42 ± 17 mmol; $p < 0.05$) despite an 18% reduction in exposure. Neither formulation increased K^+ excretion.

Conclusions: Torsemide ER prolongs urine drug levels, thereby increasing the time spent with effective drug concentrations, reduces post-diuretic Na^+ retention and moderates a fall in GFR. It caused significant Na^+ loss even during very high salt intake. Thus a short duration of action limits salt loss with loop diuretics. These conclusions warrant testing in patients with edema and heart failure.

Key words: diuretics; heart failure; sodium; kidney

CLINICAL PERSPECTIVE

What is new?

- This cross-over study in 10 normal volunteers consuming a high salt intake revealed that an extended release formulation of torsemide doubled the daily loss of sodium and fluid compared to the standard immediate release preparation.

What are the clinical implications?

- This is the first demonstration that a single dose of a loop diuretic can cause negative salt balance in subjects consuming a high salt intake.

INTRODUCTION

The prevalence of hypertension, congestive heart failure (CHF) and chronic kidney disease (CKD) is increasing relentlessly. [1] Cardiovascular disease (CVD) is the most common cause of death and disability worldwide, [2] thereby encumbering a huge economic burden. [3] Diuretics are the first line of treatment for these common conditions. The therapeutic effect of diuretics is dependent on a loss of body Na^+ and fluid. [4] Thus, their effects must be predictable if the burden of CVD is to be reduced.

The GFR is reduced in most patients with edematous conditions, mandating the use of loop diuretics since these agents have the most potent acute pharmacological action of natriuresis and diuresis.

Despite their unrivaled acute natriuretic effectiveness, loop diuretics have been rather disappointing therapeutic agents. They have several adverse effects including electrolyte and metabolic disturbances and reduction in glomerular filtration rate (GFR). [5, 6, 7, 8, 9, 10] . Furosemide causes little reduction in blood pressure (BP) in hypertensive patients with preserved renal function. [11, 12] Loop diuretics are usually preferred for patients with chronic kidney disease. However, less natriuretic drugs such as thiazides are usually preferred to treat patients with hypertension. Furosemide suffers from poor and highly variable bioavailability that is worsened in decompensated CHF [13, 14] and this may account, at least in part, for the unpredictable effects of

furosemide in treating patients with CHF. [14] Bumetanide is even more short acting. This has prompted suggestions that furosemide be replaced as the loop diuretic of choice by the more predictable torsemide, that is eliminated largely by metabolism, has a high bioavailability even in CHF and CKD and which causes little or no hypokalemia. [7, 9]

The short duration of action of 2-4 hours of all loop diuretics after oral dosing is a class defect that can lead to three problems. First, the urinary concentration of the loop diuretic resides within the therapeutic range for only a short period.[10, 15] Second, the abrupt, but short-lived, natriuresis leaves about 20 hours for the kidney to regain the salt and water lost before the next daily dose. [8, 16, 17, 12, 18, 19] These attributes accounted for the failure of furosemide or bumetanide to cause net Na^+ loss over 1-3 days of once daily administration to normal subjects unless dietary salt was restricted to below 120 mmol·day^{-1}. [8, 16, 18] Third, the torrential acute diuresis ("Niagara effect") can cause incontinence in subjects with impaired bladder control. [20]

We studied a novel extended release (ER) formulation of torsemide that delivers the drug into solution over 8-10 hours (Figure 1) to test the hypothesis that the inability of a single dose of a loop diuretic to deplete the body of salt and water during a high salt intake is due to a limited duration of action on the kidney. We compared the effects of 20 mg of oral torsemide as an immediate release (IR) or extended release (ER) formulation given to 10 healthy volunteers consuming a fixed high salt diet containing 300 mmol Na^+ daily. We measured pharmacokinetics, creatinine clearance (C_{CR}) and patterns of electrolyte and water excretion after drug administration to assess the mechanisms of any differences.

METHODS

Drug Formulation: This study compared torsemide IR (Demadex Rx) with a novel release (ER) formulation prepared by Sarfez, Inc. as a matrix-based extended release (ER) formulation with specific ratios of hydroxypropyl methylcellulose to microcrystalline cellulose. The IR preparation delivered >80% of the drug into solution within 1-2 hours whereas the ER released this fraction over 10-12 hours (Figure 1).

Subjects: Ten healthy volunteers, aged 21 to 45 years were recruited. Each gave informed consent to participate. The study was passed by the LiLine Hospital Ethics Committee, Basaveshwara Nagar, Bangalore-560079. It was assigned the DCGI, India (equivalent of the USFD) number: T-BE-296/13. Subjects were not selected on the basis of sex or race/ethnic background. They had no significant past medical history, were not taking medications, and had normal values for blood urea

nitrogen, serum creatinine (S_{Cr}), plasma electrolytes, liver function tests, hemogram, and urinalysis. All had a blood pressure (BP) less than 140/90 mmHg. Their body weight (BWt) ranged from 61.2 to 73.0 kg.

Trial Design: Each subject received both of the torsemide formulations in a randomized crossover design separated by a 3 week washout period. Neither the subjects, the investigators nor those analyzing the results were aware of the allocation to IR or ER formulation.

Subjects were pre-consented, admitted to the study unit, and received fixed constant daily meals for 3 days containing 300 mmol of Na^+ and 45 mmol of K^+. Subjects remained in the metabolic ward throughout without visitors. Each meal was observed to ensure that all the food was consumed. This provided strict control of Na^+ and K^+ intakes. Fluid was allowed *ad libitum*. Blood pressure (BP) and heart rate (HR) were taken using an automated device after 2 minutes of sitting. Subjects fasted for 12 hours prior to receiving the diuretic on day 3, and for 4 hours thereafter to allow for pharmacokinetic (PK) studies in the fasting state. To compensate for reduced salt intake (50 mmol of Na^+) during the breakfast period, they received 233 mL of 0.154 M saline solution immediately prior to drug administration. During day 2 and 3 (the day before and the day of the diuretic), subjects collected a 24-hour urine with additional recordings of timed excretion after the diuretic. Immediately before ingestion, and for 24 hours thereafter, blood and urine samples were taken at designated times. Aliquots of 2 mL of the urine were taken for analysis and the remainder added to a 24 hour collection. Blood and urine were sampled at 30 minute intervals for 3 hr after diuretic administration (0 to 3 hr); then hourly (3 to 4 hr), then 2 hourly (4 to 14 hr) and finally at 14 and 23 hr. At zero time, they received 20 mg of torsemide (IR or ER) with 330 mL of water. After completion of the study, subjects' BP and heart rate (HR) were recorded in the sitting position and they were discharged.

Analyses: Urine samples were measured for volume and 1 mL aliquots taken for measurement of Na^+, K^+ and creatinine concentrations in an automated apparatus and 1mL for torsemide concentration. Plasma and urine samples were extracted and analyzed for torsemide by a validated capillary zone electrophoresis method that recorded no signal in pre-drug samples of urine and plasma.[21]

Statistics: Mean ± SEM data were calculated for each drug period in each individual subject. To test the hypothesis, within subject paired t-tests were used to assess differences in 24 hr excretion of Na^+ and fluid after the IR versus ER preparations. The multiple P values reported for differences in parameters at different times after torsemide ER and IR were considered descriptive of the patterns of change observed after the two formulations. A P value < 0.05 was considered statistically significant.

RESULTS

All 10 subjects completed both arms of the trial without any adverse effects.

The patterns of fluid excretion (UV), creatinine clearance (C_{Cr}) and Na^+ and K^+ excretion following diuretic administration are shown in Figure 2. The UV and $U_{Na}V$ increased rapidly with the IR and ER preparations to a maximum by 1.0 to 1.5 hr respectively (Figure 2A and 2C) and remained similar until 2.5 hr after which the excretions were higher with ER than IR until about 12 hours when excretion was low with both formulations. UV and $U_{Na}V$ fell below prior levels by 4 hr after the IR, but not until 12 hr after ER. Potassium excretion (U_KV) increased sharply with both preparations and remained elevated for about 4 hr (Figure 2D) but, after 12 hours, fell to levels mostly below the prior day in both groups. There was an initial sharp increase in C_{Cr} during the first 0.5-1 hr after administration of both IR and ER torsemide (Figure 2B), but this returned promptly to baseline and was reduced below baseline at 2 hours where it remained thereafter.

The pharmacokinetic data are shown in Table 1. Compared to IR, the C_{MAX} with ER was reduced 69% and the overall AUC was reduced by 18-21%. The T_{MAX} of ER was prolonged >3-fold. There was a 59% reduction in AUC from 1 to 3 hours but a 97% increase in AUC from 8-10 hours.

The plasma torsemide concentrations rose rapidly after IR to peak within 1 hr, but the peak was delayed to about 3.5 hr after ER (Figure 3A). Thereafter, the concentrations declined log-linearly, but were several-fold higher after ER throughout the remainder of the day. Renal torsemide excretion followed a similar time course (Figure 3B). The relationship of increases in $U_{Na}V$ above basal values to the log of renal torsemide excretion (an index of natriuretic effect related to the delivery of drug to its active site) showed marked hysteresis (Figure 3C). There was a sharp rise in $U_{Na}V$ with log torsemide excretion during the initial ascending phase followed by an inflection and a much reduced natriuresis relative to torsemide excretion during the declining phase.

Subjects spent twice as long in the early ascending phase after torsemide ER than IR. This resulted in a greater natriuretic efficiency as indexed by change in Na^+ excreted per log torsemide excreted (Figure 3D).

The mean changes for 24 hours after torsemide IR or ER, compared to the prior 24 hours, and the mean differences between the changes produced by the two formulations are shown in Figure 4. Fluid excretion was not significantly changed after IR, but was increased after ER resulting in a 2.2-fold greater fluid loss of 906 mL (Figure 4A). The $U_{Na}V$ was increased after both IR and ER, but was 2.2-fold greater after ER (Figure 4B). The increase in $U_{na}V$ did not differ whether torsemide ER or IR were given as first exposure or after the 3 week washout period. $U_{na}V$ with torsemide ER on first and second exposure: +89 ± 16 vs +106 ± 18 and with torsemide IR: +48 ± 18 vs +37 ± 20 $mmol \cdot day^{-1}$. Neither drug changed 24 hour U_KV (Figure 4C). The C_{Cr} was reduced by 25% following IR, but was not significantly changed following ER (Figure 4D). BWt was reduced only after the ER (Figure 4E). Neither IR nor ER changed mean blood pressure (MBP) but there was a significant difference between the two with a small net fall of 4 mmHg after ER vs IR (Figure 4F).

DISCUSSION

The main new findings from this study of normal subjects are that a novel ER formulation of torsemide that delivers the drug into solution over 10-12 hours, prolonged the natriuresis and diuresis, doubled the loss of fluid, body weight and Na^+ without a significant fall in GFR. The diuresis was followed by sustained renal fluid and Na^+ retention but this post-diuretic period was shortened after torsemide ER from about 18 to about 12 hours. Neither formulation led to a significant loss of potassium. The ER formulation prolonged the time to maximal plasma torsemide concentration by 3.5 fold with a corresponding reduction in torsemide AUC at 1 to 3 hours of 59%, but a doubling of AUC at 8-10 hours. The overall exposure to torsemide ER was reduced by 18%. The more gradual rise to peak renal torsemide excretion prolonged the time that the drug remained in the highly effective ascending phase of the hysteretic relationship between increase in urinary Na^+ excretion above basal and log renal torsemide excretion, thereby increasing Na^+ excreted per unit torsemide excreted (natriuretic efficiency). Thus, torsemide ER reduced post-diuretic Na^+ reclamation, maintained GFR and enhanced natriuretic efficiency that together resulted in greater Na^+, fluid and body weight loss after a single dose despite a somewhat reduced bioavailability.

The 300 mmol daily Na^+ intake matched prior studies with furosemide. [8,16] The IR formulation of torsemide (20 mg) did not induce fluid or weight loss and led to a modest net Na^+ loss of 42 mmol. Similar studies with furosemide (40 mg) or bumetanide (1 mg) demonstrated no overall fluid, weight, or Na^+ loss at 24 hr after dosing [8,16] despite similar initial large increases in Na^+ excretion. The significant, albeit modest, Na^+ loss with torsemide IR in this study may relate to the slightly increased duration of natriuresis of about 4 hours compared to 2-3 hours after furosemide or bumetanide.

Two factors have been identified to account for the failure of loop diuretics to induce a consistent loss of Na^+ and fluid without dietary salt restriction. First, Brater and colleagues [15] related this to the limited time during which the urinary diuretic concentrations are within the 25 – 75 % of maximal effective concentration ("most efficient" concentration). This period was increased from about 2 hours after torsemide IR to about 4-8 hours after torsemide ER (Figure 2). Second is a prolonged post-diuretic period of Na^+ and fluid retention [8,16] that can fully offset even an intense initial short-lived natriuresis unless dietary salt is restricted. [8,16] While some negative Na^+ balance occurs with moderate (120 mmol·day^{-1}) or severe (20 mmol·day^{-1}) restriction of dietary Na^+, [18] this is difficult to achieve in clinical practice. This may account for the disappointing effects of loop diuretics as antihypertensive agents [11] or as drugs to treat uncompensated CHF. [9] The present findings that an ER formulation of torsemide induced fluid, body weight and Na^+ loss, despite a 300 mmol·day^{-1} Na^+ intake suggests that this may be the first loop diuretic formulation that does not require dietary salt restriction and monitoring of Na^+ intake (from Na^+ excretion) for efficacy.

Hypokalemia is a prominent adverse effect of furosemide, bumetanide, and thiazide diuretics. Torsemide does not routinely reduce S_K and, in the rat, prevents thiazide-induced K^+ loss. [22] Neither formulation of torsemide increased K^+ excretion significantly in this study. The absence of kaliuresis after torsemide may relate to blockade of the mineralocorticosteroid receptors [23] or reduction of aldosterone secretion. [24] The absence of hypokalemia and the high and predictable bioavailability have led to the suggestion that torsemide be the preferred loop diuretic. [9,7,13,25] Indeed, patients randomized to torsemide relative to furosemide for uncompensated CHF had a reduced rate of readmission for recurrent CHF, and a more cost effective treatment. [25]

The remarkable and rapid development of within-dose tolerance may underlie the modest or indeed non-significant increase in Na^+ excretion with a continuous intravenous infusion of a loop diuretic compared to an equivalent single oral dose. [26,27] Thus, intravenous infusion is not a reliable strategy to enhance natriuresis despite continuous delivery of the diuretic to its site of action.

Furosemide given to normal subjects reduces the 24 hour C_{Cr} by about 23%, [8] which is comparable to the pattern observed after torsemide IR in this study. A fall in GFR will compromise the fluid and salt depleting actions of the diuretic. [28] The cause for the fall in GFR is unclear, [5,11] but the GFR was better preserved after torsemide ER. Whether this will translate into better preservation of renal function during long-term therapy with torsemide ER requires study.

Prior studies reported that a slow release formulation of furosemide had a somewhat improved antihypertensive efficacy [29,30,31,32,33] but the low and variable bioavailability was worsened which led to its abandonment. Two extended release formulations of torsemide have been developed. One was abandoned and the other improved antihypertensive efficacy only very modestly and failed to improve fluid or electrolyte excretion likely because it prolonged T_{max} only slightly. [34,35,36]

We acknowledge some limitations. First, subjects were equilibrated to Na^+ intake over two days whereas we had previously used 3 days [8,16,17]. However, during prolonged fixed levels of Na^+ the individual 24 hour Na^+ excretion varies considerably. [37-39] Importantly, the daily meals were identical during the two phases of the protocol. Therefore, differences in Na^+ excretion with torsemide ER vs IR cannot be ascribed to differences in Na^+ intake. Second, this study has a limited sample size of 10 subjects. It should be followed up in a larger study of a group of patients with edema.

In conclusion, an ER formulation of torsemide that increases drug delivery into solution from 2 to 12 hours doubled daily fluid and Na^+ loss and mitigated significant reductions in GFR. Further studies over a more prolonged period in target patient populations will be required to test whether these short term beneficial effects in healthy subjects translate into enhanced therapeutic efficacy.

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Disclosures: Salim Shah is the Founder and Director of Sarfez Inc. and Peter U. Feig is the Chief Medical Officer. Christopher Wilcox is the Chief Scientific Advisor of Sarfez Inc.; Bertram Pitt is a consultant and he and Craig Brater contributed to study design and interpretation. Drs. Wilcox and

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Table 1. Pharmocokinetic Parameters after Administration of Torsemide:

Immediate Release (IR) or Extended Release (ER)

Parameter	IR	ER	P value
C_{MAX}	2962	905	<0.001
$(ng \cdot ml^{-1})$	± 412	± 93	
AUC_{0-t}	6493	5125	<0.001
$(hr^{*} \cdot ng \cdot ml^{-1})$	± 688	± 552	
AUC_{o-inf}	6728	5543	<0.001
$(hr^{*} \cdot ng \cdot ml^{-1})$	± 704	± 565	
T_{max}	1.03	3.53	<0.001
(hr)	± 0.13	± 0.27	
AUC_{1-3}	2966	1225	<0.001
$(hr^{*} \cdot ng \cdot ml^{-1})$	± 294	± 161	
AUC_{8-10}	203	400	<0.001
$(hr^{*} \cdot ng \cdot ml^{-1})$	± 32	± 50	

Mean ± SEM values (n = 10 per group)

Figure Legends:

Figure 1. Torsemide dissolution *in vitro*. Mean values (n=2) for delivery of torsemide from 20 mg tablets into a stirred solution of 0.154 mol•1^{-1} NaCl at 37°C. Solid circles and continuous lines, immediate release (IM); open circles and dashed lines, extended release (ER).

Figure 2. Fluid and electrolyte excretion and creatinine clearance after torsemide. Mean ± SEM values (n=10 per group) comparing responses to 20 mg of torsemide immediate release (continuous lines) or extended release (dashed lines). Panel A, urine flow; panel B, creatinine clearance; panel C, sodium excretion; panel D, potassium excretion. The mean values for the previous 24 hours are indicated by the horizontal dotted lines. Comparing values at the same time points after dosing with torsemide immediate release (IR) or torsemide extended release (ER): *P<0.05; **P<0.01; ***P<0.005.

Figure 3. Torsemide kinetics and relationships to natriuresis. Mean (± SEM values) for plasma torsemide concentration (Panel A), renal torsemide excretion (Panel B), changes in sodium excretion related to renal torsemide excretion (log scale) (Panel C) and torsemide natriuretic efficiency (Panel D) comparing torsemide immediate release (IR) (solid circles) with torsemide extended release (ER) (open circles).

Figure 4. Excretion of Fluid (Panel A), sodium (Panel B) and potassium (Panel C), creatinine clearance (Panel D), body weight (Panel E) and mean blood pressure (Panel F). Individual paired values for the changes in the 24 hours after torsemide from the prior 24 hours, comparing immediate release (IM) (open boxes) and extended release (ER) (crosshatched boxes) and differences (solid boxes) in the changes produced by torsemide ER vs IR. Significance of difference from prior, pre-diuretic day: *, p<0.05; **, p<0.01; ***, p<0.005. Significance of difference between changes with ER vs IR: † p<0.05