welcome Ring et al. to provide a scientifically valid explanation as to how one can account quantitatively for all the causes of the dysnatremias resulting from factors that do not alter the value of the \((N_a + K_e) / \text{TBW}\) term in the Edelman equation such as (1) changes in the \([Na^+]_p\) due to inter-compartmental water shifts due to non-\(Na^+\) and non-\(K^+\) osmotes such as hyperglycaemia, mannitol, sucrose, maltose and contrast agents; (2) transcellular shifts of \(Na^+\) and \(K^+\) in hypokalaemia-induced hyponatraemia and (3) a component of the \(N_a\) and \(K_e\) is osmotically inactive and incapable of modulating the \([Na^+]_p\) [7–9]. Moreover, based on the measured \(N_a\), \(K_e\), TBW and \([Na^+]_{pw}\) in Edelman’s study [2], the ratio of \((N_a + K_e) / \text{TBW}\) is significantly greater than the \([Na^+]_{pw}\). Given that the ratio of \((N_a + K_e) / \text{TBW}\) is significantly greater than the \([Na^+]_{pw}\), we welcome Ring et al. to provide a mathematical explanation as to how one can equate the ratio of \((N_a + K_e) / \text{TBW}\) to the \([Na^+]_{pw}\) if the slope and \(y\)-intercept of the Edelman equation were to be 1 and 0, respectively (as argued by Ring et al.).

Ring et al. also argue that our new formula ‘would not be much helped’ since it requires frequent monitoring of urinary \(Na^+\), \(K^+\) and \(H_2O\) losses to guide further adjustments in the fluid prescription. We disagree with this simplistic view. We feel that taking a quantitative approach to adjusting the rate of fluid administration based on ongoing urinary losses is a more logical approach than simply guessing blindly at the rate of fluid administration. Moreover, consideration of ongoing urinary hypotonic loss is particularly relevant in the treatment of hypernatraemia, since ongoing urinary loss of \(H_2O\) in excess of \(Na^+\) and \(K^+\) induced by furosemide would tend to result in a worsening of the hypernatraemia if not accounted for.

Lastly, Ring et al. also questioned why our patient did not exhibit the expected increased \(Na^+\) excretion. Although the urinary \([Na^+]\) was not excessively high \(([Na^+]_{\text{urea}} = 63 \text{ mmol/L})\), our patient did exhibit a significant natriuresis \((479 \text{ mmol of } Na^+ \text{ excreted})\) since the total urinary output was \(\sim 7.6\) L. Indeed, reliance on urinary \([Na^+]\) as an estimate of urinary \(Na^+\) excretion can be misleading since urinary \([Na^+]\) is not only a function of the quantity of \(Na^+\) excreted but also a function of the urinary volume excreted.

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Oral calcium load and fractional intestinal calcium absorption

Sir,

Heinrich et al. [1] examined the effect of calcium carbonate intake, as compared to that of sevelamer intake, on intestinal calcium absorption and urinary calcium excretion in healthy human volunteers. The authors reason that under steady-state conditions urinary calcium excretion ‘corresponds’ to calcium load in healthy subjects. This statement is correct for adult individuals but only for net calcium absorption from the gut, that is taking into account total intestinal calcium absorption minus calcium entering the gut lumen via intestinal, biliary and pancreatic secretions. The authors claim that by determining urinary excretion of calcium they are able to measure ‘fractional intestinal absorption’ of calcium. We think this claim is incorrect. To determine fractional intestinal absorption one has to use an isotope method, administering either a single calcium isotope [2] or two different calcium isotopes [3] together with ‘cold’ calcium and then calculating fractional absorption based on radioactivity decay in the blood. The best way to determine net absorption is to carry out balance studies. Admittedly, these methods are time and energy consuming.

When Heinrich et al. acutely switch their healthy volunteers from a dietary calcium intake of 36 mmol/day to 76 mmol/day, by adding 40 mmol/day elemental calcium in the form of calcium carbonate, the individuals are no longer in the steady state for at least some days. Following changes in calcium intake, long-term balance studies have shown that a delay of at least 30 days is necessary to reach the steady state [4]. Under non-steady-state conditions, urinary calcium excretion does no more reflect oral calcium intake.

Considering the above two shortcomings, it is not surprising that the estimates of fractional calcium absorption values in their healthy volunteers, in the presence or absence of an additional oral calcium load, namely 8.7–14.8%, are much lower than the values that are generally reported in the literature using validated methods, namely 20–40% [5,6].
Finally, the finding that serum calcium does not change in response to calcium carbonate loading is not unexpected since the organism has invented powerful mechanisms allowing serum ionised calcium to be maintained within narrow limits. The failure to observe a change in serum PTH can be explained by too much delayed blood sampling after the preceding calcium load. Circulating PTH needs to be measured 1–3 h after an oral calcium load in order to observe a transient decrease in hormone concentration. This has again been shown in a recent study in which the authors administered a mixed oral calcium (390 mg) and phosphate (500 mg) load to healthy volunteers and found a slight but significant decrement in serum PTH after 30, 60 and 150 min, but not thereafter [7]. Of interest, they did not observe such an early decrement in patients with chronic renal failure.

In conclusion, taking urinary calcium excretion as a measure of fractional intestinal calcium absorption in healthy subjects is unreliable.

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Reply

Sir,

In their letter, Dr Drueke and Dr Chanard criticized our assumption that under steady state conditions, urinary calcium excretion corresponds to the calcium load in healthy subjects. We agree that under steady state conditions in adult individuals urinary calcium excretion corresponds more strictly to the net calcium absorption and apologize for the confusion that has been created by the somewhat lax vocabulary. The determination of net calcium absorption under treatment with placebo, sevelamer and calcium carbonate was the primary aim of our study. We calculated the fraction of the dietary intake of calcium excreted in the urine according to Knapp [1]. We defined the ‘calcium load’ as the amount of calcium absorbed in the gut and neither excreted via intestinal, biliary or pancreatic secretion nor stored in the body, for instance in bone, soft tissue, intracellular pool, etc.

The study of Birge [2] does not indicate that a delay of at least 30 days is necessary to achieve steady state conditions as stated in the letter. These authors reported in the paper only that the fractional calcium absorption was identical after 30 days, but they did not study shorter time intervals. The ‘Methods’ section of this paper recommends 10–17 days of constant dietary intake. After a 1-week wash-out period between each treatment period, we determined the calcium excretion in the completely collected daily urine output over 7 days. The procedure was blinded, the protocol included randomization and each person served as its own control. Steady state conditions or at least comparable conditions are suggested during the three treatment periods, since during each of the different treatment periods, the daily calcium excretion was constant for 7 days—an argument against major disturbing influences.

In contrast to what had been suggested in the letter, the proportion of 8.7 or 14.8% of oral intake of calcium recovered in the urine is in agreement with the data of Knapp. In this paper, an intake of 15 mg calcium/kg body weight yielded a mean urinary calcium excretion of 18% of the ingested intake; if the dietary calcium intake was increased to 30 mg/kg/day, the mean urinary calcium excretion was 10.4% [1].

We agree with the authors of the letter that balance studies are very time and energy consuming and difficult to perform. We do not deny that double tracer methods are more precise and yield higher values for fractional calcium absorption. Unfortunately in Germany (as in some other countries), studies using radioactive isotopes are no longer allowed. By the way, it is of note that an association has been reported between the dietary calcium load and fractional calcium absorption when isotope methods have been combined with quantitative determination of calcium in diet, faeces and urine [3]. One has to be aware that such acute measurements of fractional calcium absorption rate are influenced not only by age, growth and sex but also by intestinal passage time, solubility of the calcium compound, acidity in the gut, compounds inhibiting calcium absorption such as oxalate or phytate, composition of the diet, action of parathyroid hormone probably via vitamin D metabolites, various diseases like hypothyroidism or hyperthyroidism, intestinal disease, etc. In this context, it is correct that our measurements of PTH do not exclude such small changes of iPTH levels shortly after food intake as reported by Isakowa few weeks ago [4]. This was, however, not the primary aim of the study and does not change our final results.