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The predictable effect that renal failure has on H2 receptor antagonists—increasing the half-life along with increasing prescribing errors

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In this edition of NDT, Manlucu et al. [1] present results from a systematic review they performed on dose reducing of histamine 2 receptor antagonists (H2RA) in the presence of renal failure. Fundamentally, they demonstrate that H2RA should be given in lower doses as renal function deteriorates. These results in themselves are not surprising as H2RA are primarily excreted in the urine unchanged, and there is substantial evidence that clearance is reduced with renal failure [2–4]. The more surprising result is that these authors managed to identify 16 published clinical studies investigating an entirely predictable pharmacokinetic occurrence, including one published as recently as 2003. The implication of this is that despite the expected effect renal failure would have on the half-life of these drugs, this class of medication continues to be prescribed at inappropriately high doses or frequency. The inappropriate prescribing of H2RA has been demonstrated in a study performed in 1996 on 100 consecutive patients receiving the drug intravenously.
In this cohort, 26 patients had an estimated creatinine clearance of <50 ml/min, with only one patient having the dose reduced. While this study is almost 10 years old, there has probably been little change in prescribing habits as adverse drug events continue to be common, and prescribing errors are a frequent culprit [6].

The clinical significance of prescribing excessive doses of H2RA depends upon the sum of the added costs and the adverse drug events. Anti-ulcer medications account for a considerable proportion of drug sales, and even though proton pump inhibitors account for the majority of these sales, H2RA remain a significant factor [7]. In a single centre, it was also shown that correct dosing of intravenous H2RA could produce considerable cost savings [5]. Manlucu et al. describe four studies that demonstrated a 2–4 times increased risk of adverse drug events resulting from inappropriately high dosing in renal failure. These adverse drug events manifested primarily as an alteration in mental status.

The results of the meta-analysis suggest that for all H2RA there may be a predictable increase in both area under the curve (AUC) and half-life with specific levels of renal function. For example there is a 300% increase in AUC when the GFR is 20 ml/min and a 200% increase when the GFR is 30 ml/min, compared to a GFR of 80 ml/min. While such a predictable rise is attractive as it implies relatively simple dose changes for any H2RA with a particular change in renal function, following this approach may be fraught with danger. The meta-analysis was performed on relatively few clinical studies with a heterogeneous small total population, and included the use of multiple different H2RA.

Including different agents in the meta-analysis does not account for differences in the pharmacokinetics between different agents. The authors attempted to compensate for this by analysing the changes in AUC and half-life rather than in the absolute values. However, different H2RA agents have varying proportions of renal versus non-renal clearance, ranging from 65% for ranitidine up to 90–95% for nizatidine [2,3]. Differences also exist in the rate of renal clearance between different H2RA agents, 304 ml/min for famotidine versus 489–512 ml/min for ranitidine [2]. As only the renal clearance will be affected by a change in GFR, the changes in AUC and half-life will be different between agents, but will still follow a predictable pattern. This is reflected by the variable recommended percent dose reductions for the different H2RA agents. In addition, the bioavailability of nizatidine is lower in uraemic patients, but is largely unchanged for other H2RA [4].

The one negative effect of dose reducing in renal failure is the potential for achieving inadequate blood levels of the drugs. The effectiveness of suppression of gastric acidity is directly related to H2RA blood levels, so this may lead to therapeutic failure.

**Methods to overcome preventable adverse drug events**

Preventable adverse drug events are a widespread problem that is not restricted to H2RA [6]. In a systematic review of the literature, adverse drug events occurred in 0.7–6.5% of hospitalized patients, with 56.6% being judged as preventable [6]. In addition, 2.4–4.1% of hospital admissions were due to adverse drug events, with 69% believed to be preventable. The majority of these preventable adverse drug events were due to prescribing errors, including ordering, transcribing, dispensing and administering errors.

There are a number of potential interventions that could be implemented to reduce adverse drug events; however, a recent survey demonstrated that there are also multiple barriers to achieve the necessary improvements [8]. Relatively sparse scientific research has been performed in this area, compared to the amount performed on the diagnosis and treatment of disease. The one area of great interest is the role that information technology could play in reducing adverse drug events [9]. Chertow et al. [10] investigated the use of a computerized order entry plus decision support system for the prescription of medications in patients with renal failure, and compared it to the usual computerized order entry. They demonstrated a significant increase in improved drug dosing and a reduced mean length of stay with the addition of a decision support system.

With the frequency of adverse drug events secondary to preventable causes, such as prescribing errors, it is important that we now concentrate our efforts on developing techniques to reduce its occurrence. Widespread use of computerized order entry systems that include decision support would seem to be the best direction to head. However, further scientific research on its benefits along with an economic evaluation of its costs would be needed.

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**References**


