The Role Of Diuretics In The Intensive Care Unit: A Review

A Haji

Citation

Abstract
Diuretics are drugs which cause a net loss of sodium and water from the body by net action on the kidney. Their primary effect is to decrease the reabsorption of sodium and chloride from the filtrate, increased water loss being secondary to the increased excretion of salt. There are various classes of diuretics which differ considerably in chemical derivation, efficacy, sites of action, and mechanism of action; namely, their pharmacology and pharmacodynamics. Effective use of diuretics requires knowledge of the pharmacology of each diuretic agent coupled with an understanding of the pathophysiology of the patient's disease. Diuretics have various uses in clinical conditions including oedematous disorders and hypertension, treatment of hypercalcaemia with loop diuretics, treatment of diabetes insipidus or hypercalciuria with thiazide diuretics, treatment of glaucoma with carbonic anhydrase inhibitors, and treatment of cerebral oedema with osmotic agents.

The use of diuretics in the acute care setting is an area of significant clinical and laboratory research. Diuretics represent one of the most commonly used agents in the intensive care unit and fluid balance occupies a significant amount of attention by the intensivist and the anaesthetist.

The author's aim was to systematically review the literature regarding the use of diuretics in critically ill patients on the Intensive Care Unit. We searched MEDLINE (1966-2004), EMBASE (1974-2004) and the Cochrane Controlled Trials Register (CCTR) to identify randomised controlled trials, in order to review the risks and benefits of diuretics in four different groups of patients. These included subjects with acute renal failure, congestive heart failure, severe head injury and also preterm infants with respiratory distress syndrome.

ACUTE RENAL FAILURE
Acute renal failure (ARF) represents a significant and persistent problem with serious implications in critically ill patients and is the most common reason for seeking nephrology consultation in the Intensive Care Unit (ICU). The reported prevalence is between 3% and 30%, depending on the definition of ARF and the case mix of the studied patient population. The prognosis is particularly ominous in patients admitted to the ICU and in whom ARF appears as part of the multiple organ dysfunction syndrome. For example, mortality in these patients was reported to be 45% in nonseptic ARF patients and as high as 75% in patients with septic ARF.

There are several theoretical arguments which support the use of mannitol and loop diuretics for the prevention or treatment of acute renal failure. Both of these agents can induce a diuresis, potentially washing out obstructing debris and casts. Mannitol may preserve mitochondrial function by osmotically minimising the degree of post-ischaemic swelling and by scavenging free radicals. Loop diuretics have been shown to improve medullary oxygenation, presumably because they selectively decrease oxygen use in this portion of the tubule by blocking active transport. The ensuing decrease in energy requirements may protect the renal cell in ischaemic conditions. In addition loop diuretics may act as renal vasodilators. Although the mechanisms above have been postulated, it remains unclear how this theory relates to actual pathophysiology in individual patients.

Several clinical studies have examined the use of loop diuretics in patients with ARF. Mehta et al analysed the outcome of all intensive care patients with ARF who received nephrology consultation in four teaching hospitals over a six year period. Patients who received loop diuretics or a combination of thiazides and loop diuretics at the time of nephrology consultation were compared with a group of similar patients who did not receive diuretics. Diuretic use...
was associated with a 68% increase in in-hospital mortality, and a 77% increase in odds of death or non recovery of renal function. The increased risk was mainly observed in patients who were relatively unresponsive to diuretics. This is the only study which suggested that the use of diuretics was harmful to patients but it is also possible that these diuretics are more frequently used in patients who would have done worse anyway. The deleterious effect noted by Mehta et al could also be due to diuretics converting oliguria to non oliguria and therefore may have delayed the recognition of ARF or underestimated its severity. This in turn may have delayed the time for obtaining consultation of the nephrologists or initiation of dialysis. However, it should also be noted that in 12% of the patients diuretics were only prescribed after the nephrology consultation.

In the Mehta study, it was also surprising that the poor results were more frequent in patients who did not respond to the diuretic challenge. It seems that the intensivist would contact the nephrologists earlier for patients who remain oliguric after a diuretic challenge, so that dialysis would have been started earlier in oliguric patients. The paper gives no further information on the causes of death, the time interval until starting dialysis, or the type of dialysis, therefore it is possible that the higher mortality was not associated with diuretic use but may have been related to the dialysis therapy.

Furthermore, there is also wide variation in the physiological parameters of hydration in the patients included in this study suggesting that many of them were not adequately hydrated, despite receiving diuretics. In addition, the nephrology consultation was also requested late in the course, when the serum creatinine was on average 3.6 mg/dl (318umol/l) in patients who received diuretics and 4 mg/dl (354umol/l) in those who did not. The mean age and prevalence of congestive cardiac failure and respiratory failure were also higher among those patients who received diuretics. This would suggest that these patients may have been more ill compared with the control group, but both groups had similar Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores. However, scoring systems such as these are not terribly reliable in ICU patients with ARF.

Two further randomised controlled trials involving 66 and 58 patients with established acute tubular necrosis have examined the use of loop diuretics in patients with ARF. These revealed that high doses of frusemide can induce a high urine output converting oliguric renal failure to non-oliguric renal failure but this fails to reduce the need for dialysis and does not reduce mortality. Although, high doses of diuretic do not affect the prognosis of patients with ARF, conversion of oliguric ARF to non-oliguric ARF simplifies patient management. If diuresis ensues, it is associated with a more liberal fluid intake and easier administration of enteral and parenteral nutrition. This diuresis also provides prognostic information that the patient had less severe ARF.

Furthermore, Lassnigg et al also showed that a continuous infusion of frusemide was detrimental in the protection of renal dysfunction after cardiac surgery as it was associated with the highest rate of renal impairment. It seems that in the laboratory, loop diuretics such as frusemide can promote the aggregation of Tamm-Horsfall protein in the lumen of the tubules, a mechanism thought to cause intratubular obstruction, contributing to renal impairment.

Despite the limitations of all these studies, the study by Mehta et al especially is clinically important because administration of diuretics to oliguric patients is still a relatively common practice. It seems that until we have data from a good powerful clinical trial which can answer whether loop diuretics harm critically ill patients with ARF, the practice of routine administration of these agents should be discouraged and we should think twice before prescribing loop diuretics in the ICU. A trial of loop diuretics should be attempted after careful correction of the volume status, should be limited in time, and importantly should not postpone consultation with a nephrologist or an intensivist experienced in ARF. We should realise that even successful conversion of oliguria to diuresis only reflects the existence of a milder form of ARF and has no prognostic effect, and does not justify postponing dialysis when needed.

**CONGESTIVE CARDIAC FAILURE**

Congestive cardiac failure is a major cause of morbidity and mortality worldwide. Diuretics are regarded as the first line treatment for patients with congestive heart failure, irrespective of aetiology, age, sex and the individual characteristics of the patient since they provide symptomatic relief. The reduction of pulmonary congestion and oedema relieves breathlessness and consequent reductions in
peripheral oedema, hepatic distention and intestinal oedema improves patients’ well being. They provide symptomatic relief more rapidly than any other drugs for heart failure as they relieve peripheral oedema within hours or days, whereas the clinical effects of digitalis, angiotensin converting enzyme inhibitors or β-blockers may require weeks or months to become apparent.

Despite widespread clinical acceptance of the use of diuretics, there is uncertainty of the precise therapeutic efficacy because there are no large scale trials on their effects on disease progression and survival. This may be in part due to the fact that diuretics have become the standard of care for patients with heart failure, especially with symptoms of congestion. This is the main reason for the difficulty of conducting the randomised trials at this point even though the overall evidence for a mortality benefit is scarce.

Interest in clinical trials using loop diuretics and thiazides has mainly been stimulated since publication of the RALES Study in 1999 which investigated the role of aldosterone antagonists. Although aldosterone is not classically a diuretic, this raised the question in our minds about the formal evidence for loop or thiazide diuretics. The Cochrane Collaboration is currently investigating this and has published a protocol earlier in 2004 and we await their results in anticipation.

There have been smaller scale studies which have compared the continuous infusion of loop diuretics with bolus intermittent administration in patients with congestive heart failure. They can be divided into low to moderate dose studies (80 – 320 mg/24 hours frusemide) and high dose studies (690 – 2000 mg/24 hours). The duration of the actual infusion varied widely and were as follows: 30 minutes (Licata 2003), 1 hour (Bagatin 1993), 4 hours (Pivac 1998), 8 hours (Dormans 1996), 24 hours (Kramer 1996), 4 hours (Pivac 1998), 8 hours (Dormans 1996), 24 hours (Kramer 1996), 4 hours (Pivac 1998), 8 hours (Dormans 1996), 24 hours (Kramer 1996), 4 hours (Pivac 1998), 8 hours (Dormans 1996), 24 hours (Kramer 1996), 4 hours (Pivac 1998), 8 hours (Dormans 1996), 24 hours (Kramer 1996), 4 hours (Pivac 1998), 8 hours (Dormans 1996), 24 hours (Kramer 1996). The observation period while on infusion also varied from 24 hours to 12 days. This illustrates the heterogeneity of the studied samples. Nonetheless, they all showed greater diuresis in the group receiving continuous infusion compared with the bolus group. Schuller et al also showed a significant reduction in hospital stay in patients who are given a continuous infusion of loop diuretics.

The poor quality of currently available data makes it difficult to comment on differences in mortality and thus make recommendations for clinical practice. Further prospective studies involving larger patient populations and longer follow up periods may provide us with stronger evidence in the future to more adequately answer questions on this issue.

HEAD INJURY

Mannitol has been widely used in the control of raised intracranial pressure (ICP) following brain injury. A 1995 survey of the critical care management of head injured patients in United States showed that 83% of centres used osmotic agents in more than half of severely head injured patients. Furthermore, a survey in United Kingdom showed that 100% of neurosurgical centres used mannitol in the treatment of raised intracranial pressure. The effectiveness of mannitol in critical patients is considered to be well established. However, for other patients this is an area of considerable clinical uncertainty not only over the optimal treatment regimen but also over the effectiveness of mannitol as compared to other ICP lowering agents and over the usefulness of mannitol given at different stages following head injury.

The Cochrane Collaboration conducted a systematic review of randomised controlled trials that compared different mannitol treatment regimens or compared mannitol to alternative interventions or placebo, at any stage in the acute management of head injuries (Nov 2002).

Intracranial pressure directed treatment showed a small beneficial effect on mortality when compared to treatment directed according to neurological signs and physiological indicators. Smith et al showed that the relative risk for death was 0.83 (95% CI 0.47, 1.46) and that for severe disability was 0.88 (95% CI 0.55, 1.38). The allocation concealment was by the use of sealed envelopes and was adequate to prevent fore-knowledge of treatment, and was unlikely to have lead to bias. However, the sample size was small. It must also be noted that the ICP-directed protocol initiated mannitol only when the ICP rose to above 25mmHg and therefore these results cannot be extrapolated to ICP-directed protocols that initiate mannitol at a lower level.

High dose mannitol appears to be preferable to conventional dose mannitol in the preoperative management of patients with acute intracranial haematomas. However, there is little evidence about the use of mannitol as a continuous infusion in patients with raised intracranial pressure in patients who do not have an operable intracranial haematoma. Cruz et al showed fewer deaths in the high dose mannitol group with a pooled relative risk of death of 0.55. They also illustrated that the proportion of patients who were dead or
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Diuretics may accelerate lung fluid absorption and improve pulmonary mechanics in these infants. The two mechanisms responsible are an immediate diuresis-independent lung fluid reabsorption secondary to systemic and pulmonary venodilatation, and also a delayed increase in urine output thereby decreasing extracellular volume.

A recent Cochrane review (2004) assessed the risks and benefits of administration of a loop diuretic in preterm infants with or developing chronic lung disease. They concluded that in preterm infants < 3 weeks of age, frusemide administration had either inconsistent effects or no detectable effect. However, in infants > 3 weeks of age, a single intravenous dose of 1mg/kg of frusemide improves lung compliance and airway resistance for one hour. Chronic administration improves both oxygenation and compliance.

Most of these studies focused on pathophysiological parameters and did not assess effects on important clinical outcomes or the potential complications of diuretic therapy. Further randomised trials are needed to assess the effects of frusemide administration on survival, duration of ventilatory support and oxygen administration, length of hospital stay, potential and long term complications. In view of this lack of data, routine administration of diuretics in this patient group cannot be recommended based on current evidence.

References

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There were no trials which compared mannitol to other ICP lowering agents except Schwartz et al compared administration of phenobarbionate with mannitol in patients with known raised ICP. Unfortunately, this yielded an imprecise effect measure and comparisons could not be accurately performed.

The timing of administration was further evaluated by Sayre et al. They compared the pre-hospital administration of mannitol with placebo in patients with moderate and severe head injury. The study was randomised and allocation concealment was through pharmacy prepared blinded solutions. Interestingly, this showed an increase in mortality amongst the mannitol treated patients (RR=1.75). However, this yield is imprecise owing to the small sample size and could be compatible with no difference, or even a beneficial effect with mannitol.

There seems to be so many unanswered questions regarding the optimal use of mannitol following acute traumatic head injury. The widespread use of mannitol, and the lack of clarity regarding optimal administration present an ideal opportunity to conduct further well designed randomised control trials.

PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME (RDS)

In preterm infants with RDS the reduction in total gas volume results from alveolar oedema more than from atelectasis. The oedema initially results mostly from inadequate clearance of foetal lung fluid and by three hours of life results mostly from proteinaceous alveolar oedema. The four factors which contribute to this include a low colloid osmotic pressure; an increase in microvascular transmural pressure resulting from increased surface tension; high hyaline membrane permeability; and reduced lymphatic drainage from the lung.

Interestingly, infants with RDS often present with an oliguric phase, followed by a spontaneous diuretic phase typically occurring at 24-72 hours that tends to precede the improvement in lung disease. This led to the hypothesis that diuresis-induced decrease in extracellular volume improves interstitial lung oedema and severity of the lung disease.

Diuretics may accelerate lung fluid absorption and improve pulmonary mechanics in these infants. The two mechanisms responsible are an immediate diuresis-independent lung fluid reabsorption secondary to systemic and pulmonary venodilatation, and also a delayed increase in urine output thereby decreasing extracellular volume.
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Author Information
Amyn Haji, MA MBChir MRCS
Specialist Registrar General Surgery, William Harvey Hospital, East Kent NHS Trust