# The Dose Makes the Poison*

*Marc M Perreault*

IV fluid therapy is ubiquitous in hospitals. It is part of any patient's admission orders, either as resuscitation therapy for patients receiving emergency or postoperative care and patients with sepsis or as maintenance therapy for patients with compromised oral intake; alternatively, IV fluid may be used as the diluent for most parenteral medications administered to patients. IV fluids are not usually purchased or stocked by the department of pharmacy, and we hospital pharmacists often do not view them as medications, with a dose–response relationship, or as a cause of potential harm to our patients. Despite the guidelines of the UK National Institute for Health and Care Excellence (published in 2013 and updated in 2017),[1] which outline general principles for managing IV fluids, they continue to be poorly prescribed overall.[2,3] The time has come that we pharmacists change our mindset about fluids and start considering this form of therapy as we would any other medication, that is, a treatment requiring individualization and proper monitoring.

A conceptual model for fluid therapy has been proposed to help prevent its inappropriate use.[4] This model consists of 4 distinct phases of fluid therapy, starting with rescue (resuscitation), proceeding to optimization and stabilization, and ending with de-escalation, thus mimicking the decreasing severity of illness over time.[4] During each of these phases, individualization—in terms of type of fluid and amount provided—is required to maintain organ perfusion while minimizing significant "third spacing". There is increased recognition of the detrimental consequences of giving too much fluid, as well as giving too much of the same fluid (e.g., normal saline [0.9% sodium chloride]), to patients.[5-10]

We have all either witnessed or been involved in cases where too much fluid was administered, for example, patients admitted from the emergency department and ending up on a medical or surgical floor days later with an excess of fluid, in the amount of 5 L or even up to 10 L. These patients have typically undergone aggressive resuscitation with boluses of fluid and are also given maintenance fluids; as their hemodynamic condition stabilizes and the inflammatory cascade abates, diuresis begins on its own or an intervention is required to initiate diuresis (e.g., administration of a loop diuretic or institution of renal replacement therapy). Unfortunately, this approach seems to be the usual and expected patient trajectory during a hospital stay; in other words, "the patient needs to swell before getting well."

This aggressive approach with fluids has been promoted through early goal-directed therapy aimed at providing fluids and vasopressors according to defined protocols in the management of severe sepsis and shock.[11] Prompt implementation of such protocols has resulted in significant improvement in clinical outcomes[11] and is currently a best practice within the Surviving Sepsis Campaign.[12]

However, evidence is now emerging of potential harm associated with providing too much fluid (positive fluid balance) to critically ill patients. Several retrospective studies have found an association between positive cumulative fluid balance at discharge from the intensive care unit (ICU) and death (whether in the ICU or elsewhere in the hospital),[5,6] raising the possibility that intervening on fluid balance might improve patient outcomes.[7] At this point, it is only an association, and no causation is implied; however, the evidence is building. In a recent systematic review and meta-analysis of randomized controlled trials and observational studies, Silversides and others[8] showed that a conservative fluid strategy in patients with sepsis or acute respiratory distress syndrome increases the number of ventilator-free days and reduces the ICU length of stay with no change in mortality, relative to a more liberal fluid strategy or standard care, setting the foundation for large randomized trials to determine optimal fluid strategies in critical illness.

*Paracelsus, dritte defensio [*Third Defense*], 1538.

In most circumstances, the fluid of choice for resuscitation, maintenance, and dilution of medications remains normal saline, also referred to as physiologic fluid. It contains 154 mmol of sodium and chloride and has a pH of 5.5. As such, it is anything but physiologic and on that basis, should be considered abnormal rather than "normal". A well-known metabolic complication of administering too much saline is hyperchloremia and its associated non-anion gap metabolic acidosis. Over the last decade, the potential for inducing acute kidney injury by chloride overload from normal saline has been recognized. However, 2 recent large clinical trials comparing saline and balanced crystalloids have failed to prove such a link.[9,10] For now, the optimal crystalloid remains to be determined.

It should be obvious that I do not pretend to solve any of the controversies associated with fluid therapy, but I do want to emphasize the growing evidence that too much fluid (in general) and too much normal saline (in particular) do not represent optimal pharmacotherapy. However, the optimal doses of fluids and of normal saline for a patient are currently unknown.

In addition, there are specific issues regarding fluids that we pharmacists face and that deserve to be addressed. The first is the need to recognize when to de-escalate fluid therapy, similar to the need to reduce a broad-spectrum antibiotic in a patient whose infection is improving. Triggers exist for giving fluid as a bolus, such as the presence of shock, a drop in systolic blood pressure, or a rise in serum lactate. However, triggers for slowing or stopping maintenance fluids have not yet been defined. For me, initiation of diuretics by the team serves as a trigger to reassess maintenance fluids. Unfortunately, without such triggers, infusion of fluids is continued for longer than required, and patients experience even greater volume overload.

A second issue that is emerging in the literature is the contribution to the overall fluid balance of fluids used to dilute medications. In a large retrospective study involving critically ill patients in the United Kingdom and Canada, the largest contributor of fluids over ICU days 1 to 3 was, surprisingly, from medication (34.5% of all fluids), whereas maintenance therapy and fluid boluses accounted for about 26.5% and 24.4% of fluids, respectively.[7] A similar observation was made in a medical ICU population where medication diluent accounted for 63% of the total parenteral volume in the first 7 days of ICU admission and was responsible for a greater incidence of hyperchloremia.[13] Hence, if fluids are to be restricted, pharmacists need to acknowledge the contribution from medication diluents to the overall fluid burden and must become involved in developing fluid-restrictive strategies.

So, the next time you are participating in patient rounds, take a moment to reassess your patient's maintenance fluid therapy and consider administering medications in smaller volumes of diluent, if possible, or transitioning IV medications to the enteral or oral route. Doing so will make the fluids less poisonous!

**References**


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