SOLUTIONS FOR PROBLEM SOLUTIONS

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Anesthesiologists like to administer their medications either intravenously or by inhalation. Both methods permit rapid distribution throughout the body and give anesthesiologists the nearly instantaneous onset of effect they desire. Although most anesthetic medications are quite lipid-soluble at physiological pH, opioids, local anesthetics, and muscle relaxants for example, being weak bases, readily form aqueous solutions when the pH of the solution is rendered mildly acidic. Other medications, like propofol or the older benzodiazepines, are not easily ionized, and more creative approaches are needed to create a formulation that can be administered intravenously. Propofol is currently supplied as an emulsion, while diazepam solution contains 40% propylene glycol and 10% ethanol to facilitate its solubility.

Some older medications have recently, or will soon, become available as intravenous injections that may be conveniently administered. The purpose of this presentation is to discuss the strategies that were used to create these solutions.

Dantrolene. The effectiveness of dantrolene in reversing malignant hyperthermia was first reported in 1975, and the commercial IV formulation was first marketed in 1979. Prior to that, dantrolene powder had to be removed from capsules and solubilized with difficulty. The original IV preparation of dantrolene (Dantrium®) is still available, and a vial contains:

dantrolene 20 mg
mannitol 3,000 mg
sodium hydroxide to pH ≈ 9.5

The vial contents are reconstituted with 60 mL of water and then shaken, often for awhile, to dissolve the contents. If an 80-kg patient requires a dantrolene dose of 3 mg/kg, twelve vials of dantrolene are required, and the resulting volume is 720 mL [1]. This certainly qualifies as a problem solution.

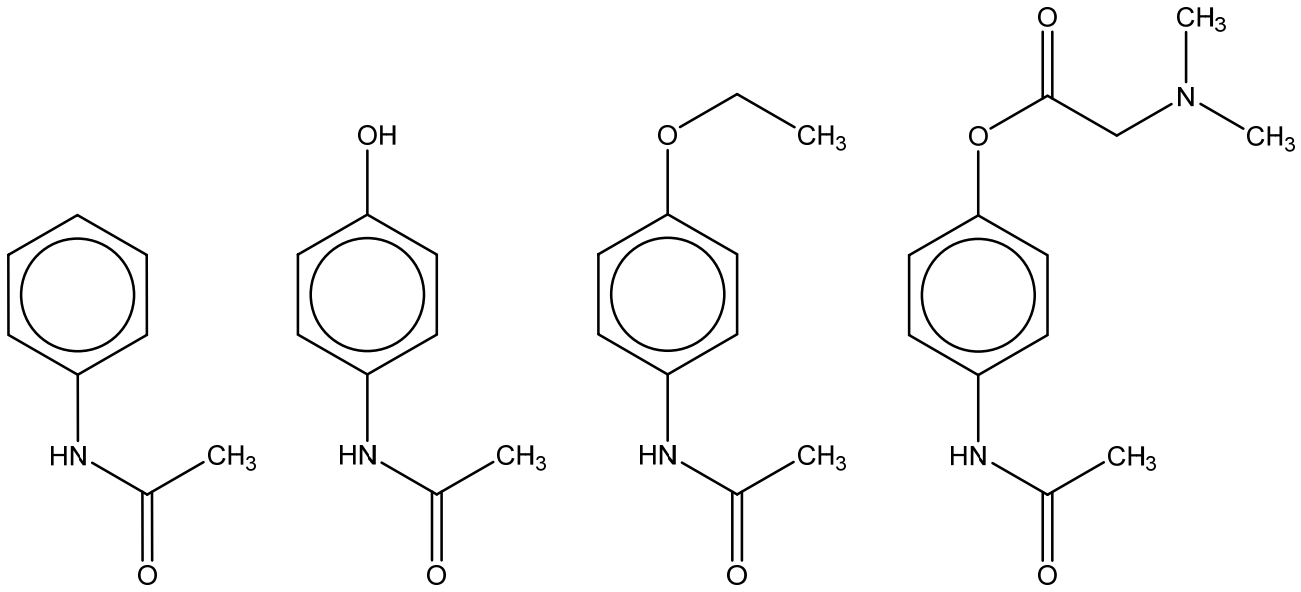
In July, 2014, a new preparation of dantrolene (Ryanodex®) was marketed. By using a combination of detergents, a much larger dose of dantrolene could be reconstituted in a much smaller volume of water in a single vial. One vial of the new preparation contains:

dantrolene 250 mg
mannitol 125 mg
25 mg polysorbate 80
4 mg polyvinylpyrrolidone
sodium hydroxide to pH ≈ 10.3

The vial contents are reconstituted with 5 mL of water, and a dose may be given as an IV bolus [2]. This new preparation represents a real solution to a problem solution. In addition to the greater ease in administration, there is an additional caveat when using the new

preparation: when giving the typical amounts of Dantrium® to treat an episode of MH, a brisk osmotic diuresis will result due to the amount of mannitol injected, although additional mannitol may be required. The amount of mannitol in Ryanodex® will not result in osmotic diuresis, and additional mannitol is required to induce the diuresis necessary to protect the kidneys from injury due to the resulting myoglobinuria. One vial of Ryanodex® currently costs about $2,300, while the corresponding dose of Dantrium® costs about $800.

Acetaminophen. Various derivatives of aniline were synthesized in the 1880's and investigated for their analgesic and antipyretic properties. The first of these to enjoy widespread use was acetanilide, however it was mostly abandoned within a decade because it produced methemoglobinemia. Acetaminophen and phenacetin were also studied, and phenacetin became widely used because of its (erroneously perceived) increased safety over acetaminophen. Phenacetin use was finally ended in the 1980's because of renal toxicity.



acetanilide acetaminophen phenacetin propacetamol

When first studied, acetaminophen, too, was thought to cause methemoglobinemia, but that was probably due to preparation contamination with nitrophenol, a synthetic precursor. Acetaminophen was "rediscovered" in the 1950's and marketed as Tylenol®. (Outside of the United States, Canada, and Japan, acetaminophen is known as paracetamol (Panadol®)). It is now known that acetaminophen is an active metabolite of both acetanilide and phenacetin and is responsible for most of the analgesic and antipyretic activity of the parent molecules.

Because of its lack of water solubility, little effort was made to develop an intravenous formulation of acetaminophen. In the 1980's, propacetamol, an ester created by linking acetaminophen and diethylglycine, was marketed in many countries as an IV formulation. It is a prodrug of acetaminophen with much greater water solubility. Interestingly, the recommended dose of IV propacetamol was twice the oral dose of acetaminophen; because the molecular weight ratio is actually about 1.6, propacetamol fared better in studies when compared to "equivalent" doses of acetaminophen.

Propacetamol is irritating when injected intravenously. In the early 2000's, there was renewed research on developing an intravenous preparation of acetaminophen. It was marketed in the United States in 2010 as Ofirmev®. The preparation contains, in each 100 mL of solution:

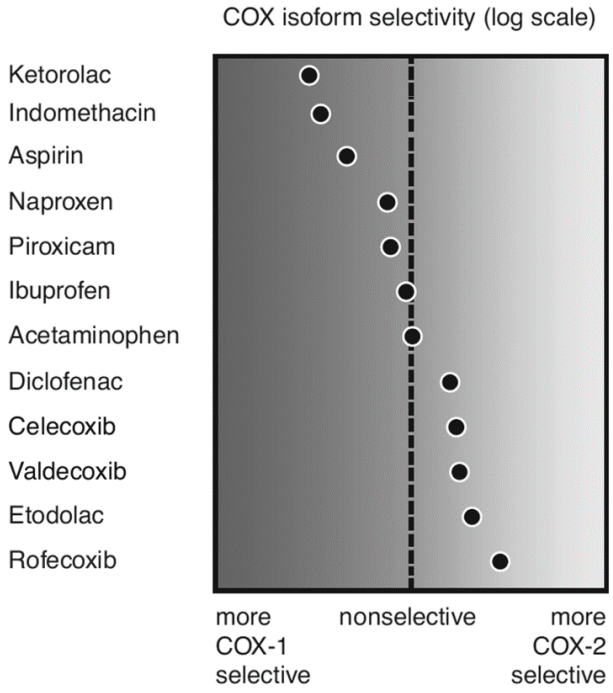
acetaminophen 1,000 mg
mannitol 3,850 mg
cysteine 25 mg
sodium phosphate 10.4 mg
pH ≈ 5.5

The 100-mL solution is intended to be given over 15 minutes [3]. Thus, as far as anesthesiologists are concerned, this solution is not a particularly good solution to a problem solution.

The package label for IV acetaminophen states, "No dose adjustment is required when converting between oral acetaminophen and OFIRMEV dosing in adults and adolescents who weigh 50 kg and above." [3] This is a true statement regarding ***toxicity***, but it may not be true in terms of ***efficacy***. Virtually all of the published clinical studies comparing oral versus IV acetaminophen have employed identical doses. However, the bioavailability of acetaminophen is not 100%; reported values typically range from 65-90%, with lower values reported for doses in the 500-650 mg range, and higher values reported for doses ≥ 1 gram.

As of this writing, the price of a 1-g dose of IV acetaminophen in the United States is about $32. (It is much less expensive in other countries). There is much pharmacoeconomic research attempting to determine the subset of patients in whom this preparation may be cost-effective.

Ibuprofen. When ibuprofen was first marketed, it was touted as a more stomach-friendly alternative to aspirin. The following graph helps explain why:



Redrawn from Goodman & Gilman, 12th ed., 2011, page 962.

COX-1-selective medications, like ketorolac and aspirin, have greater antinociceptive and antiplatelet effects while causing a higher incidence of GI ulceration. COX-2-selective medications, like diclofenac and celecoxib, have greater antiinflammatory effects while causing an increased risk of myocardial ischemia. Ibuprofen is nonselective, inhibiting COX1 and COX2 to the same degree. In comparison to aspirin and ketorolac, it does indeed cause less GI ulceration.

The oral formulation of ibuprofen was first marketed in 1974, and it became available as an over-the-counter product ten years later. In 2009, the intravenous formulation was marketed as Caldolor® [4]. A vial contains:

ibuprofen 800 mg
arginine 624 mg
water to 8 mL, pH ≈ 7.4

A vial of IV ibuprofen currently costs about $11 in the United States. It is therefore much less expensive than IV acetaminophen, while at the same time being much more expensive than IV ketorolac whose 30-mg and 60-mg vials are both less than a dollar. In contrast to parenteral ketorolac, parenteral ibuprofen should not be given IM.

Diclofenac. Diclofenac and etodolac were first marketed in 1988 and 1991, respectively. This was before the initial reports of the separate isoforms of COX in 1992, and the marketing of the first "COX-2-selective" drug, celecoxib, in 1998. However, as the graph on the previous page shows, both diclofenac and etodolac are selective for COX-2, and etodolac is in fact more selective for COX-2 than celecoxib or valdecoxib that were both marketed as "COX-2-selective" medications.

Parecoxib, a water-soluble prodrug of valdecoxib, underwent several studies in the late 1990's in the United States, but was never marketed here after valdecoxib and refocoxib were withdrawn from the market due to an increased risk of myocardial ischemia. It is, however, available in numerous other countries. Interestingly, ketorolac, so commonly used in the United States in the perioperative period, is not available in many other countries because of the increased risk of perioperative bleeding and GI ulceration.

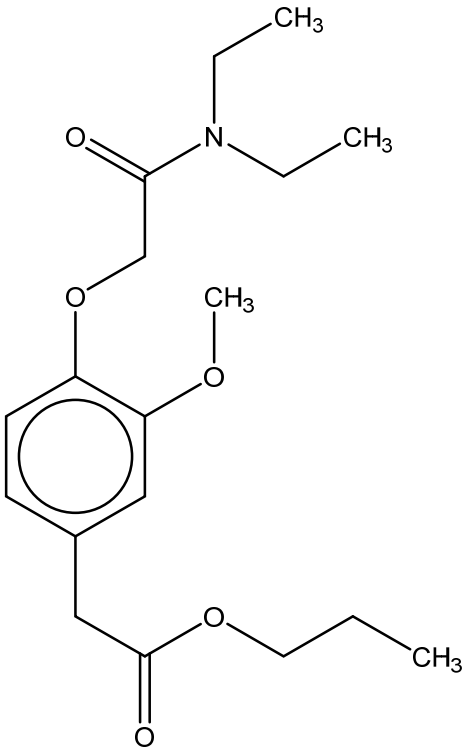
Diclofenac has long been available in other countries for IV or IM administration. The preparation is called Voltarol® and contains diclofenac 25 mg/mL along with mannitol and propylene glycol to facilitate solubility and benzyl alcohol and sodium metabisulfite as preservatives. The recommended administration method for the treatment of acute postoperative pain is to dilute 3 mL of the solution with 100 mL – 500 mL of normal saline or 5% dextrose solution to which 0.5 mEq of sodium bicarbonate has been previously added. This solution is then infused over 30 – 120 minutes [5]. This certainly qualifies as a problem solution.

There is a new, investigational solution of diclofenac (Dyloject®) that has been approved by FDA but that has not yet been marketed in the Unites States. The 1-mL vial contains:

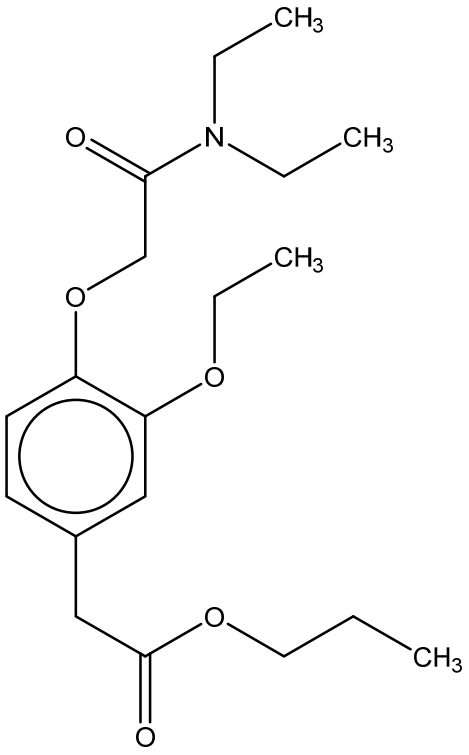
diclofenac 37.5 mg
hydroxypropyl betadex 333 mg
monothioglycerol 5 mg

A dose can be administered as an IV bolus over 15 seconds [6]. This new preparation also represents a real solution to a problem solution. It also represents one member of an expanding group of preparations in which a cyclodextrin is used to facilitate solubility.

The new preparation of IV diclofenac has been compared to IV ketorolac in a few human trials. A single-dose study compared 30 mg ketorolac with multiple doses of diclofenac in persons having third molar extraction [7]. Both the 37.5 mg and 75 mg treatment groups appeared to experience similar analgesic efficacy to 30 mg of ketorolac. Ketorolac appeared to provide a longer duration of analgesia than diclofenac, however the difference was not significant. Another study compared 18.75 mg or 37.5 mg of diclofenac with 30 mg of ketorolac, each given every six hours, for several days following abdominal or pelvic surgery [8]. In this study, analgesia from 37.5 mg diclofenac or 30 mg ketorolac was similar, and superior to that of 18.75 mg diclofenac.



propanidid



AZD3043

Propanidid. In the 1970's, there were three IV anesthetics marketed in many countries, but not in the United States, that were formulated in polyethoxylated castor oil (Cremophor®): alphaxalone, propanidid, and propofol. All three preparations were essentially abandoned because of the high incidence of hypersensitivity reactions, including full-blown anaphylaxis, attributed to the solubilizing vehicle. All three therefore qualify as problem solutions. Interestingly, polyethoxylated castor oil continues to be used in the United States as the solubilizing agent for such parenteral medications as the immunosuppressive cyclosporine and the antineoplastic paclitaxel. Prior to the administration of these medications, patients are typically premedicated with histamine H_1 and H_2 antagonists and a glucocorticoid in an attempt to decrease the incidence and severity of hypersensitivity reactions. But what became of these three IV anesthetics?

In the 1980's, propofol was, of course, reformulated as an emulsion in Intralipid®. It became a blockbuster product and largely replaced thiopental as the IV induction agent of choice because of its more rapid offset kinetics, lesser hangover effects, and intrinsic antiemetic activity. The currently available propofol preparations represent a real solution to a problem solution.

Propanidid is a natural product found in clove oil. It is rapidly metabolized by esterases and thus has superior offset kinetics to propofol. However, a well-tolerated and reliable preparation has not yet been marketed. AZD3043 contains a minor alteration to the propanidid molecule that results in higher potency. *[Important disclaimer: In 1999, I was a consultant to Advanced Medicine that later changed its name to Theravance. I suggested to Tom Jenkins, the head medicinal chemist at Advanced Medicine, that he synthesize a derivative of propanidid in order to create a drug that would be superior to propofol.]* It was formulated as a lipid emulsion and studied in rats and pigs. Presumably because of its esterase metabolism, it had superior offset kinetics to propofol [9]. This month, the first human trials of AZD3043 are being published [10-12]. As described in the accompanying editorial [13], it is still too early to decide whether the lipid emulsion of AZD3043 represents a solution to the problem solution of propanidid.

Alphaxalone. Althesin® was a formulation of alphaxalone and alphadolone in Cremophor®. A new formulation of alphaxalone, solubilized in a β-cyclodextrin, has been prepared, and the first human trial is being published this month [14]. The kinetics of this preparation of alphaxalone were found to be similar to those of propofol, but there was less of a cardiovascular depressive effect as compared to propofol. As with AZD3043, it is still too early to decide whether this formulation of alphaxalone represents a solution to the problem solution of alphaxalone.

Although the authors of the present study did not address these questions, I would like to wonder aloud what would happen if a large volume of the β-cyclodextrin vehicle were given to an individual anesthetized with alphaxalone. Would it be toxic? Would it reverse the anesthetic effects? As we know, sugammadex, a γ-cyclodextrin, binds to, and rapidly terminates the pharmacological effects of, rocuronium. Might alphaxalone be the first reversible intravenous anesthetic agent by virtue of its binding to a large excess of its vehicle? I would love to see the results from this experiment!

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