

Paying the Piper: Considerations for managing high cost antidotes

 **Background**

Reasons 



 **Pharmacoeconomics**

Risks vs Benefits 

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I have no financial disclosures to report



Background

- Large increase in price of medications
- Antidote price increases not immune to this
- Ongoing drug shortages

Objectives

- Identify some factors that drive the cost of antidotes
- Recognize the costs associated with the use of specific antidotes
- Identify resources available to determine what patients require antidotal therapy
- Recognize the role of the poison center in assisting in the stocking of antidotes as well as patient specific management

The Impact to poisoned patients

- Reduction in hospital stocking antidotes
- AWP increase of > 50% for 15 out of 33 antidotes
- Stocking price increased by > \$1000 for 8 out of 33 antidotes

Where We've Felt it Most

Antidote	2010 AWP \$	2015 AWP \$	% Change
Edetate Calcium Disodium 6 grams	746	40,391	5308
Methylene blue 900 mg	59	1,118	1786
Protamine 200 mg	8	35	341
Digoxin immune FAB 100 mg	18,213	76,3210	319
Naloxone IV 15 mg	153	317	107
Succimer 86 grams	7,692	13,291	73

Adapted from: Heindel GA et al Clin Tox 2017

Expert Consensus Guidelines for Stocking of Antidotes in Hospitals That Provide Emergency Care

Richard C. Dart, MD, PhD; Lewis R. Goldfrank, MD; Brian L. Erstad, PharmD; David T. Huang, MD, MPH; Knox H. Todd, MD, MPH; Jeffrey Weitz, MD; Vikhyat S. Bebarta, MD; E. Martin Caravati, MD, MPH; Fred M. Henretig, MD; Theodore R. Delbridge, MD, MPH; William Banner, MD, PhD; Sandra M. Schneider, MD; Victoria E. Anderson, MPH*

*Corresponding Author. E-mail: victoria.anderson@empdc.org.

- Is the antidote effective?
- Do the benefits outweigh its risks?
- Is time an important factor?
- Does the antidote need to be immediately available?
- Does the antidote need to be available within 60 minutes?
- What amount of the antidote is needed to treat one 100 kg patient?

Dart et al. Ann Emerg Med 2017

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*Corresponding Author. E-mail: victoria.anderson@mpdc.org.

- 45 antidotes were considered for stocking
- 2447 articles were utilized to develop the recommendations

- 44 antidotes were recommended to be stocked
 - 17 antidotes added from previous recommendations
- 23 antidotes recommended for immediate availability
 - Opioid poisoning
 - Cardiac glycoside toxicity
 - Cyanide poisoning
 - Methemoglobinemia
- 14 antidotes recommended within 60 minutes

Dart et al. Ann Emerg Med 2017

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What Factors Are Involved?



What Factors Are Involved?



Why do drugs cost what they cost?

- Research and Development
- Marketing
- Licensing Fees to FDA
- Liability Fees to FDA

- Low Utilization Drugs
- Orphan Drugs

"Hidden" Fees

- Prescription Drug User Fee Act (PDUFA) in 1992
 - Authorized the FDA to collect fees for its review for new drugs
- Numerous other fees including inspection and registration activities

- New Drug Application PDUFA: \$2,374,200
 - New Drug Application Establishment: \$585,200
 - Annual Product Registration: \$114,450
- Generic Drug User Fee Act (GDUFA): \$76,030
- Liability Fees: upwards of \$500,000

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Is it only the Price Tag?

- Direct costs
- Indirect costs
- Reimbursement fees

Pharmacoeconomics

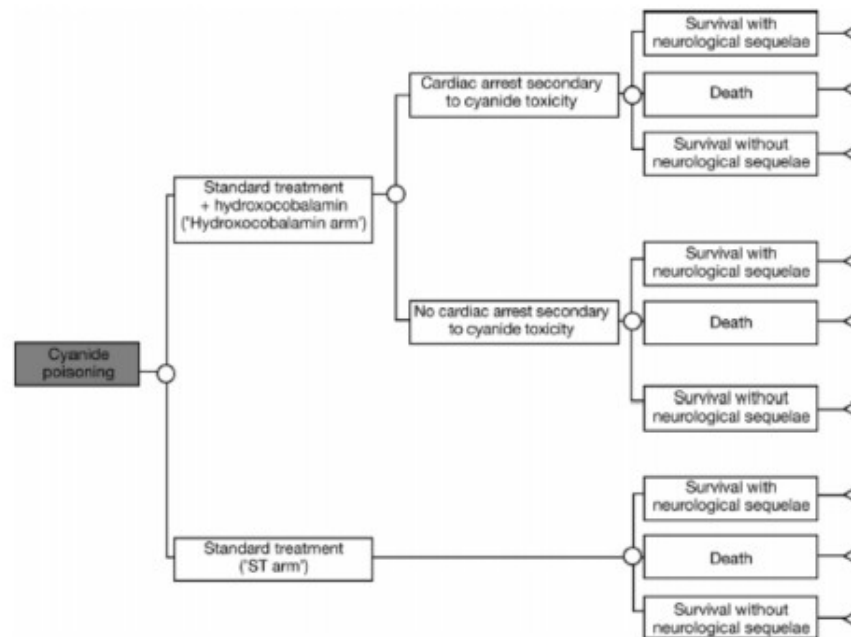
Concepts:

- Cost-benefit
- Cost-effectiveness
- Cost-minimization
- Cost of illness
 - Cost of adverse drug events
- Cost-utility

Arenas-Guzman R et al. J Eur Acad Dermatol Venereol 2005; 19 Suppl 1:34-39
DiMasi JA et al. Pharmacoeconomics 2001; 19(7): 753-766

Antidotes & Pharmacoeconomic Comparison

Decision Tree Analysis



Drieskens S, et al. *Eur J Hosp Pharm* 2013;0:1-7. doi:10.1136/ejpharm-2012-000213

Antidotes & Pharmacoeconomic Comparison

Antidote	Cost Analysis	Conclusions
NAC	<ul style="list-style-type: none"> • IV versus PO comparison • Total cost associated with hospital stay 	<ul style="list-style-type: none"> • PO > IV for hospital stay <ul style="list-style-type: none"> • 7 days vs. 4 days • \$18,287.63 vs \$7,607.82
Hydroxocobalamin	<ul style="list-style-type: none"> • Treatment vs standard treatment 	<ul style="list-style-type: none"> • Hydroxocobalamin could save 17 lives per year • Better neurologic outcomes and less death • "Acceptable" levels of cost effectiveness
Fomepizole	<ul style="list-style-type: none"> • Compared the cost per adverse drug event avoided • Fomepizole versus ethanol 	<ul style="list-style-type: none"> • Cost Effectiveness ratio • \$10,521 for ethanol • \$5,169 for fomepizole

1. Martello JL et al. Cost minimization analysis comparing enteral NAC to IV NAC in the management of acute acetaminophen toxicity. *Clin Tox* 2010; 48: 79-81
2. Drieskens S et al. Belgian cost effectiveness analysis of hydroxocobalamin in known or suspected cyanide poisoning. *Eur J Hosp Pharm* 2013; 0:1-7
3. Marreffe JM et al. Cost-effectiveness of fomepizole versus ethanol in the management of acute ethylene glycol exposure. *Clinical Toxicology* 2005; 43(6): 691.

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What if cost didn't matter?

- Efficacy
- Risk of ADRs
- Utility of certain antidotes

Some Cases for Consideration

2 yo male

- Crying
- Inconsolable





Scorpion Envenomations

- Increased Morbidity
- Symptoms:
 - Pain; parasthesias
 - Cranial nerve deficits
 - Tongue Fasciculations
 - Hypersalivation
 - Slurred Speech
 - Involuntary shaking/jerking extremities
- Sedation and Pain Control
- ICU Admission
- Duration of symptoms: 12 - 30 hours

Centruroides F(ab')₂ (Anascorp)

Administration of antivenom:

- 31 minutes vs 22.2 hours for resolution of symptoms
- Children < 2 yo: 14 min for symptom resolution

Cost:

- AWP: \$3,000-4,000 per vial
- Reports of hospitals charging: \$7,000 to \$39,000 per vial

LoVecchio F et al. Clin Tox 2003; 41(7)
O'Connor AD et al. Clin Tox 2017

Is Antidote Cost Worth It?

Is the cost of the Fab Antidote worth it?

A Case

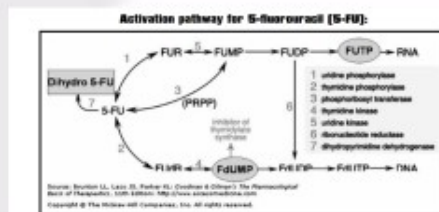
2 year old male is found with an empty tube of Efudex(R) 5%. The tube was originally 40 grams and was full.

The ingestion occurred approximately 30 minutes earlier.

What would you do?

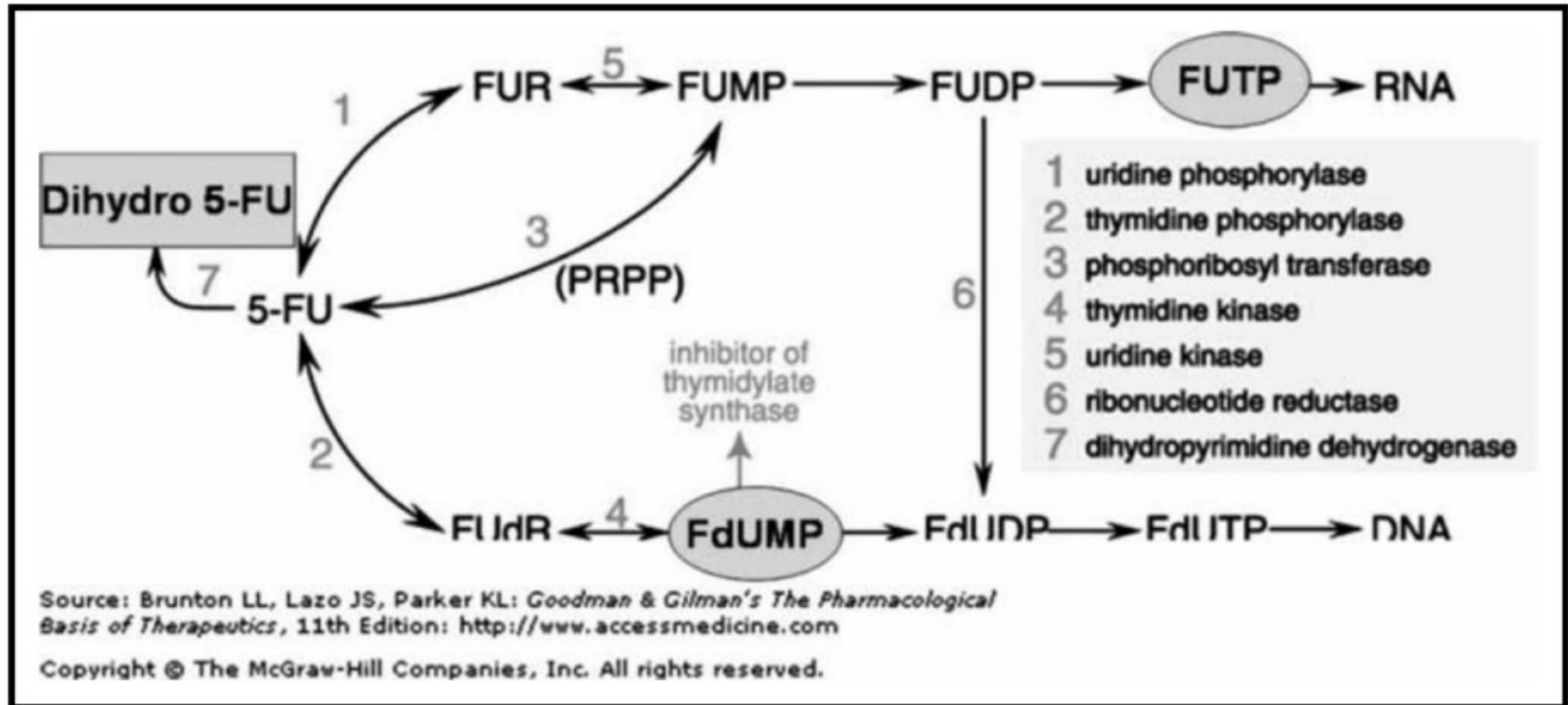
5-Fluorouracil

Doses > 5 mg/kg result in severe toxicity



Uridine Triacetate (Vistogard):
Oral Prodrug
Course of therapy: \$75,000
Drop shipped from Wellstat/BTG
Pharmaceuticals

Activation pathway for 5-fluorouracil (5-FU):



Uridine Triacetate (Vistogard):
Oral Prodrug
Course of therapy: \$75,000
Drop shipped from Wellstat/BTG
Pharmaceuticals

A Case

55 year old male presents to the ED after a fall. He is awake and alert.
HR 110 bpm; BP 120/70 mmHg; RR 15/minute; 98% saturation RA

He has a tib-fib fracture and has to go to the OR

PMH: DVT x2; on dabigatran 150 mg twice daily

The ED is asking if Idarucimab should be administered before the OR?

Idarucizumab?

CLINICAL TOXICOLOGY, 2017
<https://doi.org/10.1080/15563658.2017.1349911>

 Taylor & Francis
Taylor & Francis Group

 Check for updates

SHORT COMMUNICATION

Incomplete dabigatran reversal with idarucizumab

Aaron P. Steele , Jin A. Lee and William E. Dager

Department of Pharmacy Services, University of California, Davis Medical Center, Sacramento, CA, USA

ABSTRACT

Context: With increasing use of direct oral anticoagulants (DOACs), urgent reversal of these agents becomes a growing concern. Idarucizumab is a humanized monoclonal antibody fragment that specifically binds to dabigatran with higher affinity than thrombin, rapidly neutralizing its anticoagulant effect without increased risk of thrombosis.

Case details: We describe two cases in which the recommended dose of idarucizumab was unsuccessful in completely reversing the anticoagulant effects of dabigatran. Both of these patients were noted to have supratherapeutic international normalized ratios (INRs) and high dabigatran concentrations. In the first case, an 86-year-old male underwent an emergent procedure and experienced excessive hemorrhaging refractory to blood product repletion, idarucizumab, and factor eight inhibitor bypass activity (FEIBA). In the second case, a 62-year-old female in shock was found to have elevated dabigatran concentrations despite two doses of idarucizumab, continuous renal replacement therapy (CRRT), blood product repletion, and FEIBA. Both patients ultimately expired from their coagulopathies.

Discussion: These cases illustrate the potential for incomplete reversal of dabigatran with the recommended 5 g of idarucizumab and emphasize the importance of early detection of dabigatran toxicity. While direct dabigatran serum concentrations are not readily available, the INR may be a useful surrogate marker for supratherapeutic dabigatran concentrations.

ARTICLE HISTORY

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KEYWORDS

Dabigatran; idarucizumab;
international normalized
ratio; reemerging; reversal

2-2.5 gram vials
= ~\$4,000

Case

3 year old male with developmental delays is sent to the ED by his pediatrician

- PICA
- Venous Blood Level = 55 mcg/dL

Decision to initiate chelation is made

- BAL Plus edetate calcium disodium
- OR
- DMSA (succimer)

Remember Back....

Edetate Calcium Disodium: \$40,391 (for 6 grams)

DMSA: \$13,291 (for 86 grams)

Normal Doses of Chelators:

DMSA 30 mg/kg/day

Sodium Calcium Edetate 75 mg/kg/day

REVIEW

A comparison of sodium calcium edetate (edetate calcium disodium) and succimer (DMSA) in the treatment of inorganic lead poisoning

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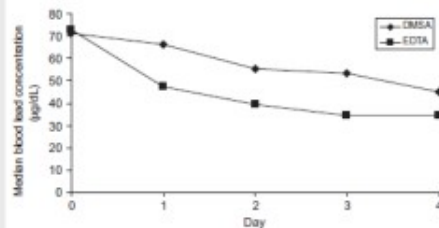


Fig. 4. Median blood lead concentrations during chelation with oral DMSA 30 mg/kg/day ($n = 32$) or sodium calcium edetate 75 mg/kg/day ($n = 8$). Although sodium calcium edetate (34.5 µg/dL) reduced blood lead concentrations to a greater extent than did DMSA (45 µg/dL) by day 4, the difference was not significant ($p = 0.79$) (based on Bradberry et al.⁶ and Bradberry¹⁴).

Both are effective
One is likely not superior

What if there were endless resources and cost didn't matter?

Dart RC et al. Expert Consensus Guidelines for Stocking of Antidotes in Hospitals that Provide Emergency Care. Ann Emerg Med 2017

What if there were endless resources and cost didn't matter?

- Dantrolene
- Digoxin immune Fab
- Hydroxocobalamin
- Fomepizole
- Various Antivenoms
- DMSA/BAL
- Uridine Triacetate
- Glucarpidase
- NAC

Dart RC et al. Expert Consensus Guidelines for Stocking of Antidotes in Hospitals that Provide Emergency Care. Ann Emerg Med 2017

Long Term Solutions



ACMT Position Statement: Addressing the Rising Cost of Prescription Antidotes

Disclaimer: While individual practitioners may differ, these are the positions of the American College of Medical Toxicology (ACMT) at the time written, after a review of the issue and pertinent literature.

Antidotal therapy is an essential component of poisoning management. In recent years, there have been unprecedented increases in the costs of antidotes. The American College of Medical Toxicology calls upon providers, hospitals, formularies, pharmaceutical industry, government, insurance companies and pharmacy benefit managers to adopt practices to ensure that antidotes are available to our patients, and priced based on value and cost.

Background:

Antidotal therapy is an essential component of management of suspected or actual poisoning. Hospitals must also stock antidotes to meet emergency preparedness obligations.¹ Per capita prescription drug spending accounts for 17% of healthcare costs, an amount greater than for any other nation.² In recent years, there have been unprecedented and profound increases in the costs of antidotes and other prescription drugs in the U.S. The causes of the high costs of pharmaceutical products are multifactorial and closely tied to market and regulatory factors.

November 2017

Long Term Solutions

- Regional sharing of costly antidotes
- More rigorous pharmacoeconomic studies
- Poison Center's and Toxicologist can assist and be an integral part of decision making process

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