Pharmacological Review of Medical Aid in Dying (MAiD)

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Statement of the Problem

- A variety of drugs have been used for MAiD with current regimens developed empirically.
- Foundational principles in pharmaceutics, pharmacokinetics, and pharmacology can inform decisions regarding MAiD drugs.

Purpose

This evidence-based project reviewed MAiD drugs in the context of pharmaceutical, pharmacokinetic and pharmacological principles.

Background

Drugs used for MAiD have evolved. Early drugs were used predominantly on the basis of availability to the patient. Once MAiD became legalized, drug choices were made by a small number of physicians and then used widely.

Goal of MAiD is a peaceful death within 1-2 hours with no disturbing adverse effects.

Progression of Prescribed MAiD Drugs

Secobarbital or Pentobarbital
Diazepam+Morphine+Propranolol
Digoxin+Diazepam+Morphine+Propranolol
Digoxin+Diazepam+Morphine+Amitriptyline
Digoxin … Diazepam+Morphine+Amitriptyline

Methods

- Targeted literature searches were conducted in series.
- Goals and drugs used for MAiD were identified from lay and professional publications and discussion with pharmacists.
- Scientific foundations were established based largely on tertiary literature.
- Searches were conducted for individual drugs, their chemical and pharmacokinetic properties, and the relationship of individual MAiD drugs to foundational principles.
- Video recordings were identified that confirmed and extended earlier information.

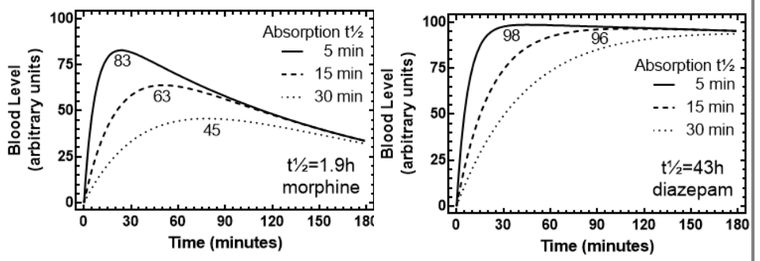
Findings & Implications

Scientific Foundations

Absorption is the process of drugs passing through a biological barrier to enter the systemic circulation.

For MAiD formulations, drugs are typically present as a solid suspension. Each drug must enter solution before being absorbed through passive diffusion, which is directly proportional to surface area for absorption and the concentration of unionized drug. The chemical properties of drugs (size, pKa, $P_{o/w}$) influence absorption.

Peak blood concentrations depend on how rapidly a drug is absorbed, particularly with drugs having a shorter elimination $t\frac{1}{2}$.



Drug Name	mol wt	pKa	$P_{o/w}$	Absorption	Elimination
secobarbital	238.28	7.8	1.97	90% bioavailable $t\frac{1}{2}$~20min peak:3h	29h (15h - 40h)
pentobarbital	226.27	8.11	2.1	100% bioavailable peak: 1h	15h - 50h
diazepam	284.74	3.4	2.82	100% bioavailable peak: 1.3±0.2h	43 ± 13h
morphine	285.34	8.21	0.89	24% bioavailable peak: 0.5-1.5h	1.9 ± 0.5h
propranolol	259.34	9.42	3.48	26% bioavailable peak: 1.5h	3.9 ± 0.4h
digoxin	780.9	--	1.26	66% bioavailable peak: 1-3h	39 ± 13h
amitriptyline	277.4	9.4	4.92	45% bioavailable peak: 2-5h	20h

- Barbiturates are favored MAiD drugs based on their unique chemistry.
- Diazepam, as a base with a pK of 3.4 and good lipid solubility, is immediately absorbed starting in the stomach and acts within minutes.
- Morphine, has poor qualities for stomach absorption and will saturate opioid receptors in the intestines to slow motility.
- Digoxin is empirically administered prior to other drugs as a strategy to coincide peak concentrations with those of amitriptyline.
- Amitriptyline has been added for its synergistic toxicity but is also synergistic w morphine for GI slowing and has the slowest absorption.
- Formulation changes might improve MAiD. Administration in basic medium (eg antacid) could promote absorption of basic drugs.
- Alternative drugs might be considered based on absorption properties; fentanyl (highly potent and lipid soluble) could be formulated for rapid absorption from the oral mucosa and require lower doses than currently used for morphine dosage while decreasing the bulk of the cocktail.

Limitations

There are relatively few publications and no randomized trials of MAiD. Prescribers seem reluctant to try different drugs since an effective cocktail has been identified.

References/Acknowledgement

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Battin M, Lippman AG, eds. *Drug Use in Assisted Suicide and Euthanasia.* New York, NY: Pharmaceutical Products Press; 1996..
Berkowitz BA. The relationship of pharmacokinetics to pharmacological activity: morphine, methadone and naloxone. *ClinPharmacokinet*, 1976;1:219-30.
Dear J. The doctors who invented a new way to help people die. *The Atlantic*. January 22, 2019.
Hogben CAM, Schanker LS, Tocco DJ, Brodie BB. Absorption of ddrugs from the stomach. II. The human. *JPharmacolExpTher*. 1957;120: 540-5.
Hughes MT. The pharmacist and medical aid in dying. AmJHealth-SystPharm.2017; 74:1253-60.
Humphry D: *Final Exit*. New York, NY: Delta Random House 2010.
Martinez MN and Amidon GL: A mechanistic approach to understanding the factors affecting drug absorption: A review of fundamentals. *JClinPharmacol*, 2002;42:620-643.
Wolf SM, Berlinger N, Jennings B. Forty years of work on end of life care –from patients' rights to systemic reform. *NEnglJMed*. 2015; 372:678-82