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Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs

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HIGHLIGHTS

- Role of pollution prevention is examined for reducing drug entry to the environment.
- Eco-directed sustainable prescribing (EDSP) is proposed for reducing drug excretion.
- Drug loadings in environment via sewers are dictated by pharmacokinetics.
- Prescribing could be guided by selecting drugs that are poorly excreted.
- Do empirical environmental occurrence data for drugs correlate with pharmacokinetics?

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ABSTRACT

Active pharmaceutical ingredients (APIs) from the purchase and use of medications are recognized as ubiquitous contaminants of the environment. Ecological impacts can range from subtle to overt — resulting from multi-generational chronic exposure to trace levels of multiple APIs (such as in the aquatic environment) or acute exposure to higher levels (such as with wildlife ingestion of improperly discarded waste). Reducing API entry to the environment has relied solely on conventional end-of-pipe pollution control measures such as wastewater treatment and take-back collections of leftover, unwanted drugs (to prevent disposal by flushing to sewers). An exclusive focus on these conventional approaches has ignored the root sources of the problem and may have served to retard progress in minimizing the environmental footprint of the healthcare industry. Potentially more effective and less-costly upstream pollution prevention approaches have long been considered imprudent, as they usually involve the modification of long-established norms in the practice of clinical prescribing. The first pollution prevention measure to be proposed as feasible (reducing the dose or usage of certain select medications) is followed here by an examination of another possible approach — one that would rely on the excretion profiles of APIs. These two approaches combined could be termed eco-directed sustainable prescribing (EDSP) and may hold the potential for achieving the largest reductions in API entry to the environment — largely by guiding prescribers' decisions regarding drug selection. EDSP could reduce API entry to the environment by minimizing the need for disposal (as a consequence of avoiding leftover, unwanted medications) and reducing the excretion of unmetabolized APIs (by preferentially prescribing APIs that are more extensively metabolized). The potential utility of the Biopharmaceutics Drug Disposition Classification System (BDDCS) is examined for the first time as a guide for API prescribing decisions by revealing relative API quantities entering sewage via excretion.

1. Introduction

The practice of health care (the use of prescribed medications in particular) can have a broad spectrum of potential adverse health and economic consequences for both the environment and humans. Continuing to emerge is an understanding of the complex network of interconnected routes (Daughton, 2008; see Fig. 1 therein, also available: http://www.epa.gov/nerlesd1/bios/daughton/drug-lifecycle.pdf) that play active roles in the release to the environment of active pharmaceutical ingredients (APIs[1]) from the intended use and misuse of medications. These routes are especially important with respect to

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[1] Abbreviations — API: active pharmaceutical ingredient; BDDCS: Biopharmaceutics Drug Disposition Classification System; CAFO: confined animal feeding operation; EDSP: eco-directed sustainable prescribing; LOD: limit of detection; MEOC: Matthew Effect Orphaned Chemical; MQL: method quantitation limit; OTC: over the counter; PBT: persistent, bioaccumulative, and toxic; PK: pharmacokinetics.

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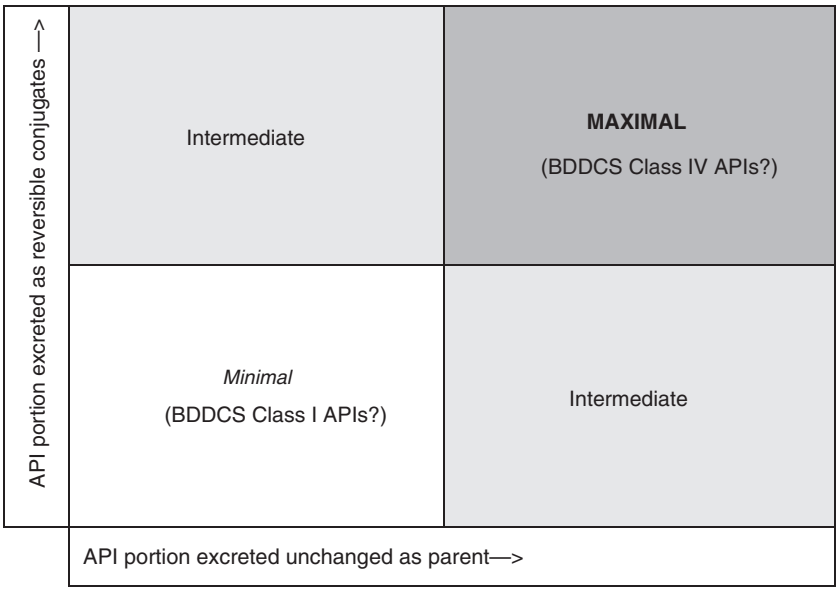

Fig. 1. Environmental loadings of APIs as a function of excretion and reversible conjugation. See Supplemental Table S-3 for a list of example APIs (and supporting references) that have shown "negative removals" during sewage treatment — often, perhaps, as a result of deconjugation. The possible predictive utility of the BDDCS is also indicated for Class I and Class IV APIs.

the aquatic environment [where many APIs have become ubiquitous trace contaminants — continuously present in many waters and displaying a pseudopersistence (Daughton, 2002, 2003; Mackay et al., in press); also see extensive list of references cited in Supplementary Tables S-1 and S-2] as well as for both the escalating defacto reuse of water (Rice et al., 2013) and the growing need for planned wastewater recycling, especially for potable use (Debroux et al., 2012). The potential for adverse impacts derives from two major routes: (1) the excretion of unmetabolized residues of APIs (as well as their active metabolites and "masked" derivatives such as metabolic reversible conjugates — the parent API linked to certain endogenous biomolecules) and (2) the accumulation of unwanted, leftover medications, whose safe and prudent disposal is often an onerous task for the consumer and rarely performed properly (Daughton, 2010a).

In general, excretion of API residues is the major route to the environment (especially for the aquatic domain), with adverse effects in the aquatic environment now known to be possible at extremely low API exposure levels. In contrast, the major concern regarding humans is non-therapeutic exposure and self-exposure to diverted leftovers via accidental, incidental, unintentional, or purposeful consumption — primarily via ingestion or dermal pathways (Bond et al., 2012; Budnitz and Salis, 2011; Burghardt et al., 2013; Daughton, 2010a). Morbidity and mortality among infants, toddlers, teens, and the elderly (from unintended exposure or non-medical self-exposure to diverted drugs, both of which are exacerbated by the incidence of leftovers) are well documented and largely preventable or avoidable. Mortality is especially notable and discouraging since it is often preventable. Additional routes for the entry of drug residues to the environment are bathing and dermal transfer. These routes could be more important than excretion for select drugs that are formulated primarily into topical preparations (such as high-content creams and transdermal devices) and for APIs that are extensively excreted via sweat; these routes may play significant roles in human bystander exposure. Bathing can transfer residues to sewers and ambient waters, while dermal contact may transfer significant residues to surrounding surfaces or directly to other people (Daughton and Ruhoy, 2009).

Historically, problems regarding chemical contaminants in the environment — especially those where sewage plays the major role — have been addressed with pollution control measures. End-of-pipe treatment is the long-established norm. Recognition has grown over the last decade, however, that myriad numbers of trace-level "emerging" contaminants (such as APIs) comprise the majority of the synthetic chemicals that remain in treated sewage, even with advanced treatment. Continual advancements needed for engineered treatment technologies capable of removing ever-lower levels of trace contaminants from solutions are resource intensive, and limits probably exist with regard to their economic sustainability (Jones et al., 2005).

Since the 1990s, various means of conventional and more advanced pollution control continue to be examined for reducing the ultimate entry of APIs to the aquatic environment, especially via treated sewage (e.g., Coday et al., 2014; Luo et al., 2014). But a singular focus on resource-intensive (and not fully effective) end-of-pipe approaches [such as improved treatment technologies for wastewater and drinking water, and "take-back" programs for collection of unwanted leftover medications to avert their disposal by flushing to sewers (e.g., Glassmeyer et al., 2009)] ignores the root origins of the problem and may actually serve to retard meaningful progress in minimizing the ecological and chemical footprints of the healthcare industry. In contrast, pollution prevention is a major unexplored approach for minimizing the impact of healthcare on the environment. Preventative measures would target the root factors that promote or facilitate the release of APIs to the environment. The most important routes for the release of APIs to the environment are excretion (unmetabolized API or active metabolites), bathing (topical APIs and sweat), and imprudent disposal of leftover, unwanted medications (especially to sewers). The key up-stream processes that dictate the scope and magnitude of excretion are the regulations, guidelines, behaviors, and customs surrounding the practice of prescribing and ultimate use, along with the associated activities of dispensing as influenced by the administration of healthcare and the insurance industry (Daughton, 2013; Ruhoy and Daughton, 2008).

1.1. Background

The practice of health care involves the widespread use of roughly 2500 distinct active pharmaceutical ingredients (APIs) in the US (roughly 4000 worldwide) formulated into tens of thousands of commercial pharmaceutical preparations (Daughton, 2013). The intended ultimate use of these APIs — some of which can elicit biological effects at the nanomolar level and below — often results in the excretion