Dose Discrepancies Between the Physicians’ Desk Reference and the Medical Literature, and Their Possible Role in the High Incidence of Dose-Related Adverse Drug Events

Jay S. Cohen, MD

Background: Adverse drug events (ADEs) are a major cause of morbidity and mortality, and even minor ADEs may adversely affect patients’ compliance with treatment. Because most ADEs are dose-related phenomena, adjusting drug dosages to account for individual patients’ needs and tolerances is fundamental to good therapeutics.

Objective: To determine whether the Physicians’ Desk Reference (PDR), the leading source of drug information for physicians, provides the full range of effective drug doses, especially the lowest, least ADE-prone doses of medications, for physicians to consider in treating patients.

Methods: Review of dosage guidelines and dose-response information in the PDR. Comparison with dose-response data obtained from articles listed in MEDLINE from 1966 to 2000.

Results: For many types of medications, physicians are frequently advised to use the lowest effective doses of drugs, especially initially. Yet, effective low doses determined in prerelease studies or in postrelease work are often omitted from the PDR, even when they have been recommended by expert panels.

Conclusions: Optimal therapeutics depends on the availability of comprehensive information. However, the PDR contains only the limited dose information from package inserts. Because the PDR was originally developed as a promotional device, there is no mechanism by which all clinically relevant dose-response data or important postrelease discoveries are regularly and rapidly incorporated into it. Thus, a gap exists in the availability of current and comprehensive dose information for physicians. This article provides information on lower, effective doses for 48 major medications, with an extensive reference list—a compilation of low-dose information not previously published, to our knowledge, in the medical literature. Physicians must have a readily accessible source of current and complete dose-response information to individualize drug therapy and minimize the risks of ADEs.

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Opinions differ regarding the extent of iatrogenic illness secondary to medication reactions, but there is general agreement that this is an important problem. The most recent meta-analysis determined that in 1994 an estimated 106000 hospital patients had fatal adverse drug events (ADEs), “making these events between the fourth and sixth leading cause of death” in the United States annually.1(p1200) The study also estimated that 2216000 hospitalized patients had ADEs that were considered serious, which the study defined as requiring hospitalization, being permanently disabling, or resulting in death. Clearly, even more ADEs occur that do not reach these levels of severity. In a recent editorial, Bates addressed questions about these statistics by stating, “Even if the true incidence of ADEs is somewhat lower than reported by Lazarou et al, it is still high, and much higher than generally recognized.”2(p1216) This statement probably represents the general viewpoint.

DOSE-RELATED ADEs

Data quantifying the percentage of ADEs that are caused by dose-related effects of drugs are limited. Goth’s Medical Pharmacology states, “Many adverse reactions probably arise from failure to tailor the dosage of drugs to widely different individual needs.”3(p98) Melmon and Morrell’s Clinical Pharmacology4 places the percentage of ADEs that are dose related at 75% to 85%. The study by Lazarou et al1 presents the most recent and extensive assessment, finding that 76.2% of the ADEs tallied were dose related.

Beyond the statistics, the study by Lazarou et al1 was unique in another important aspect: unlike previous studies, this

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study excluded errors by physicians and pharmacists. The goal was to assess ADEs that occur with standard methods of care. In doing so, the study demonstrated “that there are a large number of serious ADEs even when the drugs are properly prescribed and administered.”

Supporting these findings is an earlier study by Faich that found that of approximately 37,000 ADE reports submitted to the Food and Drug Administration (FDA) in 1985, 71% “involved toxic reactions to usual doses of drugs.” Clearly, prescribing within manufacturers’ dosage guidelines is no guarantee of avoiding ADEs.

ADEs AT “USUAL” DOSES

“Usual doses of drugs” typically refers to the doses recommended by manufacturers in package inserts. Because the drug descriptions in the Physicians’ Desk Reference (PDR) are identical to package inserts, these usual doses are also recommended in the PDR. Physicians generally accept and follow the manufacturers’ dose guidelines, because it is the drug companies that performed the pharmacokinetic, pharmacodynamic, dose-response, and clinical studies during prerelease research. Furthermore, these manufacturer-recommended doses are sanctioned by the FDA when approving the original content and subsequent changes in package inserts.

However, if more than 75% of ADEs are dose related and occur at the usual, manufacturer-recommended doses, are these doses really proper for some patients? Because so many ADEs are dose related, it is not possible that for some patients these doses may be excessive? This raises the question of how the usual doses are selected and whether they can reasonably be expected to match the broad variation in drug response among patients.

USUAL DOSES ARE BASED ON PRERELASE RESEARCH

The manufacturer-recommended doses of medications are usually selected during phase 1, early in the process of prerelease research. The studies on which dose selection is based may be brief and limited in scope, often involving 100 subjects or fewer. Thus, according to Peck et al, “the extra time needed to explore the full dose range and various dose intervals to obtain good dose and concentration information may not be committed....” 7(p117) The result is that “on too many occasions failure to define dose-concentration-response relationships leads to unacceptable toxicity or adverse effect rates, marginal evidence of effectiveness, and a lack of information on how to individualize dosing.” 7(p117) Other experts have also commented on the inapplicability of prerelease data to patients seen in everyday practice. Of course, this is not always the case, but when deficiencies do exist, they are not readily apparent to physicians based on the information provided in PDR drug descriptions.

POSTRELEASE DOSE INFORMATION

After a drug is introduced for general use—and the package insert is written and codified in the PDR—the postrelease phase of drug experience (phase 4) begins. Because phase 4 often involves millions of patients over many years, this phase can be extremely informative. Bates writes: “Only after drugs leave the trial setting and are used in sicker patients do their true risks become apparent.” 2(p1217) Phase 4 often reveals new uses for drugs or higher incidences or new types of ADEs. Phase 4 also engenders independent research that reveals the effectiveness of doses that differ from those recommended by the manufacturer. Sometimes, these doses are significantly lower and may cause fewer ADEs.

Once a lower dose is adequately studied, one would expect that this dose would be used by physicians. However, this would require that physicians receive the new information, which is not easily accomplished. Even though a low-dose study may be published, there are hundreds of journals, and physicians typically subscribe to just a few. Nor do physicians read every article of every issue they receive. Therefore, it is important that drug references commonly used by physicians incorporate the new information about lower, effective drug doses, so that this information can be disseminated in an organized, ongoing manner to improve medication therapy and prevent dose-related ADEs.

PHYSICIANS’ USE OF THE PDR AND OTHER SOURCES OF DRUG INFORMATION

The PDR is the leading drug reference among physicians (Medical Economics Company, written communication, September 23, 1999). According to surveys conducted by the Medical Economics Company (written communication, September 23, 1999), 82% to 90% of physicians consider the PDR their single most useful reference. The average US physician consults the PDR approximately 8 times per week (Medical Economics Company, written communication, September 23, 1999), an independent study found “almost daily use” of the PDR. The PDR’s extremely handy indexes, easy-to-use format, and state-of-the-art pill identification section may in part explain its popularity among physicians. Undoubtedly, another factor is that, each year, more than 50,000 PDRs are delivered free to physicians’ offices.

Other drug references have difficulty competing against the PDR, which is underwritten by the pharmaceutical industry. For example, in 1994 only 16,000 volumes of the respected AMA Drug Evaluations, which cost more than $100 per volume, were published. In 1996, the AMA Drug Evaluations ceased publication. The American Hospital Formulary Service, Drug Information 1999 contains some low-dose data, but it is sold primarily to pharmacies. Relatively few physicians purchase it. Drug Facts and Comparisons contains little low-dose data and is used primarily by pharmacists.

Other sources of information may also be underused. An article published in 1990 found little use of the “Index Medicus or computer-based bibliographic retrieval systems.” Physicians used the research literature “infrequently” and rated it least useful “in terms of credibility, availability, searchability, understandability, and applicability.” Physicians are more computer oriented today, but even with determined effort,
low-dose information is difficult to find, identify, and interpret among the millions of articles in the literature. Abstracts often fail to mention lower doses when studied with higher, manufacturer-recommended doses, and full articles frequently downplay the significance and potential utility of lower-dose formulations that manufacturers do not intend to produce.

The ineffectiveness of articles in the medical literature in altering the prescribing habits of physicians has been demonstrated time after time. More than a decade after the dangers of high-dose oral contraceptives were recognized, physicians continued prescribing these drugs to tens of thousands of women. For years, physicians continued writing millions of prescriptions for terfenadine (Seldane) after the drug’s cardiac toxicities were reported and an effective substitute, loratadine (Clarinex), became available. Surveys following the publication of new guidelines by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) have repeatedly shown not only that most physicians do not adopt the JNC guidelines but also that many who regularly treat hypertension have never heard of the JNC.

CURRENTNESS OF PDR DOSE INFORMATION

Although a new edition of the PDR is published annually, this does not mean that the individual drug descriptions are updated annually. Most are not, but this is not apparent because, unlike package inserts, PDR drug descriptions are not dated. There is no requirement for drug companies to update their package inserts or, therefore, their data in the PDR, which a decade after a drug’s approval may still be based solely on the limited prerelease data. Indeed, changes in package inserts must be approved by the FDA and may require manufacturers to conduct new studies, which in turn may discourage them from updating their package inserts. Thus, many phase 4 findings are not reflected in the PDR, and much PDR information is outdated. Some examples include the following.

**Estrogens, Conjugated**

Estrogens, conjugated (Premarin), was the most prescribed drug in the United States in 1998 (46759000 prescriptions filled) and during the past decade. Estrogen therapy causes a significant incidence of dose-related ADEs, dropouts are frequent, and estrogens may promote uterine and, possibly, breast cancer. Using the lowest effective dose has long been accepted as fundamental to avoiding ADEs, maintaining patients’ quality of life, and maximizing compliance to prevent long-term complications such as osteoporosis and fractures. Postrelease experience quickly led to the acceptance of an initial dose of 0.625 mg/d of estrogens, conjugated, for treating hot flashes and excessive sweating, the symptoms that most often prompt women to seek treatment. Respected drug references indicate that as little as 0.3 mg/d of estrogens, conjugated, is adequate for many women. In contrast, through 1999, the PDR recommended 1.25 mg/d of estrogens, conjugated, as the initial dose for treating vasomotor menopausal symptoms, a 100% to 400% higher dose than other sources and the same dose recommended 35 years earlier in its 1964 edition.

In 2000, the PDR recommendation was finally reduced to 0.625 mg/d, which may still be excessive for many women.

**Antihypertensive Drugs**

Antihypertensive therapy is often complicated by dose-related ADEs that affect quality of life and compliance. Studies indicate that 16% to 50% of patients prescribed antihypertensive drugs quit treatment within a few years. Meanwhile, significant dose discrepancies exist between the medical literature and the PDR for antihypertensive drugs. For example, for amlodipine besylate (Norvasc), the 14th best-selling drug in the United States in 1998 (with 23218000 prescriptions), the sixth report of the JNC recommends an initial dose of 2.5 mg/d. The PDR recommends 5 mg/d, a dose 100% higher than that of the JNC. Similar dose discrepancies exist for atenolol (Tenormin), hydrochlorothiazide, lisinopril (Prinivil or Zestril), ramipril (Altace), and more than a dozen others.

**Other Medications**

The PDR’s descriptions of scores of other major medications are similarly lacking in important prerelease and/or postrelease data about effective low doses. Sometimes, a manufacturer will present clinical data that support its recommended dose while omitting important data about lower effective doses. Various nonsteroidal anti-inflammatory drugs (NSAIDs) provide examples of these deficiencies.

Although many NSAID write-ups in the PDR explicitly state the importance of using the lowest dose of the NSAID with each patient, the actual low-dose data that would make this most possible are often lacking. This is important because dose-related ADEs from NSAIDs have prompted more reports to the FDA than any other drug group, and most NSAID ADEs are dose related. Annually, 8000 to 16000 deaths and 70000 to 107000 hospitalizations have been related to NSAID use. Using the truly lowest effective dose required by each patient is key to the safest use of NSAIDs.

**Ibuprofen (Motrin)**

At least 3 studies before and 6 studies after FDA approval demonstrated the effectiveness of just 200 mg of ibuprofen 3 times daily for treating postpartum uterine cramps, dysmenorrhea, postoperative dental pain, and rheumatoid arthritis. In several of the studies, this
low dose was as effective as the usual 400-mg dosage given 3 or 4 times daily. None of these data were ever mentioned in the PDR or otherwise made readily available to physicians by the manufacturer. Thus, from ibuprofen's introduction in 1974, physicians have prescribed the 400-mg dose most often, and for many years the lowest available dose was 300 mg.

### Diclofenac Sodium (Voltaren)

Diclofenac was the top-selling prescription NSAID from 1982 to 1993 and is still a popular medication. At least 6 studies before and several studies after FDA approval demonstrated the effectiveness of a dosage of 75 mg/d (25 mg given 3 times daily), as opposed to the

<table>
<thead>
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<td>Famotidine (Pepcid)</td>
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<tr>
<td>Misoprostol (Cytotec)</td>
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<td>50 or 100 µg QID</td>
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<td>Nefazodone hydrochloride (Serzone)</td>
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<td>Propranolol hydrochloride (Inderal, regular and XL)</td>
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<td>Ramipril (Altace)</td>
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<td>Ranitidine hydrochloride (Zantac)</td>
<td>150 BID or 300 HS</td>
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</tbody>
</table>

* Dose values are given as milligrams per day unless otherwise indicated. PDR indicates Physicians' Desk Reference; BID, 2 times daily; HS, at bedtime; QID, 4 times daily; TID, 3 times daily; QD, daily; QHS, every night; and XL, extended release.
† Brand names are given in parentheses.
‡ The PDR’s “usual” initial dose is 5 mg/d, but notes that 2.5 mg/d may be sufficient for “some patients.” The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends 2.5 mg/d initially for all patients.
§ For vasomotor symptoms.
|| The PDR states, “A dose of 10 mg also lowers blood pressure, but the full effect is not seen for 4-8 weeks.”

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PDR’s recommendations of 100 to 150 mg/d for osteoarthritis and 150 to 200 mg/d for rheumatoid arthritis. None of these low-dose data have ever been mentioned in the PDR.

**Celecoxib (Celebrex)**

Similar problems persist with new drugs. The manufacturer-recommended dosage for celecoxib’s most widely used indication, osteoarthritis, is 100 mg twice daily for everyone. This one-size-fits-all dose not only forces physicians to go outside of the approved guidelines when patients require dose adjustments but also ignores the significant effectiveness of a 50% lower dose. Moreover, because of its indications, celecoxib will be used by many elderly patients in whom the drug increases to 40% higher plasma levels (on average) and exhibits a prolonged half-life. Older women (>65 years), who may use celecoxib more than any other population, display an even greater accumulation of celecoxib. Yet, although many other drugs with similar plasma elevations in elderly patients are recommended at lower doses for this population, celecoxib is not. Celecoxib may prove less prone to cause gastrointestinal tract hemorrhage than older NSAIDs, but its tendencies to cause other dose-related ADEs, including renal injury, are no different. The importance of using the lowest dose needed by each patient applies just as much to celecoxib as to other NSAIDs, yet celecoxib’s one-size-fits-all dosing for osteoarthritis, the omission of important low-dose data, and the production of celecoxib in only 100- and 200-mg capsules limit physicians’ ability to adjust just-celecoxib doses according to the differing tolerances and needs of individual patients.

**COMMENT**

“The most common therapeutic intervention in medicine is writing a prescription.” The ramifications of inadequate dosing information affect all members of the medical community: patients, physicians, pharmaceutical companies, and private and public insurers. No one benefits when up to 50% of patients prescribed antihypertensive drugs and/or dropouts at the usual doses (eg, antihypertensive and antidepressant agents); (2) in nonimmediate situations in which dose titration is easily accomplished or in which ADEs may cause compliance problems; (3) in initiating treatment with patients known to be slow metabolizers, who have histories of medication intolerances at usual doses, or who are otherwise considered high risk; and (4) in initiating treatment with elderly patients, especially the very old (≥80 years) or frail or other elderly patients with multiple disorders and/or who are taking other medications.

In short, the ready accessibility of complete dose-response information would allow physicians to consider starting with a clearly defined, lowest effective dose of a drug in any therapeutic situation that is not immediate or severe. After all, if a low initial dose is not sufficiently effective for a patient, it can easily be increased. Similarly, studies should also be undertaken on whether many ADEs occur with escalating doses. If so, one solution would be to provide better, more gradual dose-escalation regimens that do not routinely require 100% increases in medication, which are large jumps pharmacologically, yet commonplace in medication therapy.

Technically, efficacy and tolerability may be separate variables of drug dynamics, but clinically, there is no opportunity to test these factors separately. Ultimately, it comes down to choosing a specific dose and testing its effect in a patient for efficacy and tolerability. Thus, each new prescription or dose adjustment is an “N of 1” experiment of its own. It is a safe assumption that, in general, a lower effective dose is likely to be better tolerated than a higher one. Therefore, complete information about dose-response and the lowest effective doses is essential for physicians and patients.

**Expediting the Flow of Current and Complete Information to Physicians**

Even if the origins of dose-related ADEs become better defined and the lowest effective doses are determined, informing physicians of this information would remain a challenge. Despite its popularity, the PDR has never conformed to the requirements of any true drug reference. The PDR was originally developed as a promotional device, not as a source of current and comprehensive drug information.

If the PDR were a minor drug reference used infrequently by physicians, its deficiencies might be unimportant. However, the PDR is the leading drug reference among physicians. The availability of the PDR on many hospital floors makes it a common resource for residents and interns. Nurses and other health professionals also rely heavily on the PDR. In addition, the PDR is...
an important drug reference for consumers, who buy more than half a million PDRs each year (Medical Economics Company, written communication, September 23, 1999), and it is the basis for much information in other professional and consumer drug references. Yet, many health professionals and consumers are not aware of the deficiencies of the PDR and that its recommendations may in fact lead to suboptimal care.

Questioning whether the PDR should be our leading reference may be worth discussion, but for now the PDR is our leading reference, and it likely will remain so in the future. Hopes that new online systems will somehow remedy these problems have not been fulfilled so far—and these systems are just as likely to rely on incomplete package insert or PDR data as other drug references have in the past. The fact is, no standard, readily available drug reference consistently offers complete prerelease and postrelease drug information for physicians’ use.

Solutions to this problem are easy to conceive, but difficult to implement. Solutions might include (1) an improved PDR containing current, complete drug information, thereby warranting its standing among physicians and consumers; (2) the adaptation of another current drug reference with comprehensive dose-response information that is made readily accessible to physicians and consumers; and (3) an entirely new reference, perhaps created from the joint contributions of physicians and their organizations, foundations, the pharmaceutical industry, and the government.

Many obstacles, especially funding problems, stand in the way. However, a reliable, comprehensive resource of drug information would be cost-effective if it facilitated improved therapeutics that minimized risks, reduced ADEs, improved compliance, and reduced the long-term consequences and costs of untreated disorders. Undoubtedly, a readily accessible, complete drug resource would become a fixture on bookshelves and computer screens. From habit, users would be able to locate information quickly and to rely on it with confidence. Links to MEDLINE and other catalogs would expedite in-depth study of any area of interest. Most important of all, the possession of complete dose-response information would also permit physicians to fulfill a primary principle of pharmacotherapy: using the least amount of medication necessary for each patient and, thereby, minimizing the risk of doing harm—the cornerstones of high-quality, preventive, ethical medical care.

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