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THE TOXICITY OF ANTI-RHEUMATIC DRUGS: PROBLEMS AND SOLUTIONS*

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Oliver Wendell Holmes, perhaps the most prominent of the advocates of therapeutic nihilism of the last century (a tradition continuing through Sir William Osler) stated eloquently that 'if all of the materia medica were wrapped up in a great net and cast into the sea, it would be all the better for mankind, and all the worse for fishes.' We recognise, of course, that there were in fact few effective medications in the pre-scientific medical era of Holmes, and we are grateful that his observations do not apply to our time.

Indeed, we have many effective medications in many drug classes. We can eradicate infections, replace missing hormones and palliate cancer. We can block most of the defense systems of the body. We can suppress cough, reduce fever, treat diarrhoea, keep the blood from clotting, stop vomiting, moderate the emotions. We can reduce pain and we can reduce inflammation. In our modern allopathic paradigm we assume that all of this is good. We avoid the questions that a modern-day Holmes would pose. Taking a broad view, and forgetting the fishes, is our world a better place, or a worse one, or just the same as a world in which a particular medication or a particular class of drugs had never been developed? What will be the view from the next century about our uses of our materia medica?

These questions are particularly apt when we consider our approaches to management of the major rheumatic diseases, rheumatoid arthritis and osteoarthritis. We have come to base these approaches overwhelmingly upon the non-steroidal anti-inflammatory drugs (or NSAIDs), drugs which are effective at reducing inflammation and at reducing pain. These drugs are collectively used in more patients than any other class of medications. And they present problems of major degree, of five general types.

NSAID frequently cause symptomatic side effects but this obvious toxicity is balanced clinically by symptomatic improvement, at least over the short-term, and need not perhaps disturb us too much. They also cause asymptomatic gastric ulcers, with a point prevalence of 25 per cent observable endoscopically. The clinical relevance of these lesions, which appear usually to heal spontaneously, is arguable. However, sometimes these ulcers bleed profusely or otherwise result in serious morbidity and mortality. They also require a large expenditure of medical resources, not merely from the cost of the medication itself but from the tests used to monitor toxicity, the other drugs required to prevent or treat co-morbidity, physician visits to monitor drug tolerance, and the hospitalizations to treat serious complications.

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ARAMIS (Arthritis, Rheumatism and Aging, Medical Information System) has for twenty years been assessing long-term outcomes in patients with rheumatic disease. Outcomes are defined and expressed in the patient's terms, under the paradigm of the five Ds (death, disability, discomfort, drug toxicity and dollar cost). In initial studies we developed the Health Assessment Questionnaire (HAQ) and validated its disability and discomfort scales. We have subsequently studied mortality in rheumatic diseases and the factors which influence it, and have examined their economic impact.

Over the past ten years as we have turned our attention to perhaps the most difficult problem, that of objectification and quantification of drug toxicity. When we began the ARAMIS Post-Marketing Surveillance Program we defined our goal as 'the asking and answering of clinically meaningful questions about the positive and negative effects of drugs which were not answered in pre-marketing studies'. We categorised such questions as (1) comparative studies of alternative drugs, (2) studies of long-term efficacy and toxicity, (3) studies of the adverse effects of drug combinations, (4) studies of the effects of comorbidity, including age, upon toxicity, (5) generalizability of pre-marketing results to non-experimental populations, and (6) definition of the characteristics of those with side effects. Absent from our goals was an attempt to identify new extremely rare side effects; by definition rare side effects can affect only a small number of individuals, while the common side effects account for the great majority of mortality and morbidity from drugs, and are clinically far more important. We planned to approach these critically important clinical questions through prospective longitudinal study of substantial numbers of patients.

Our experiences in post-marketing surveillance led us quickly to the emerging entity of NSAID gastropathy. While gastrointestinal side effects had long been associated with use of non-steroidal anti-inflammatory drugs, serious complications were generally felt to be exceedingly unusual. Still, increasing numbers of reports were focusing attention upon gastrointestinal NSAID side effects and endoscopic studies by gastroenterologists were beginning to define a specific syndrome involving mucosal and sub-mucosal pathology, most typically in the stomach but also seen throughout the gastrointestinal tract. The endoscopic lesions were reversible by prostaglandin administration and thus presumably were related to prostaglandin depletion by NSAIDs. We set out to examine the incidence of NSAID gastropathy, the frequency with which it resulted in hospitalisation or death, and the risk factors which influenced the likelihood of adverse events. From this base we sought to assess a series of possible solutions, including selective utilization of less toxic NSAIDs.[1–5]

We began to study gastrointestinal hospitalizations in nearly 3,000 patients with rheumatoid arthritis (RA), followed for nearly 10,000 patient years (Table 1). Patients were consecutively seen in a community population in Santa Clara County, California, private rheumatology practices in Wichita and Phoenix, a regional sample from Saskatchewan, and a University clinic at Stanford. One-hundred and sixteen admissions for gastrointestinal morbidity were identified, nearly all of them patients who were taking NSAIDs. The relative risk for such an admission while a patient was on NSAIDs was over five times the risk when a patient was not taking such drugs. The rate of admission for gastrointestinal disorders was 1·6 per cent per year, and the excess rate associated with use of NSAIDs approximately 1·3 per cent per year. While our extrapola-

TABLE 1

Hospitalizations for gastrointestinal disorders in 2,747 rheumatoid arthritis patients*

RA patients hospitalized with GI symptoms	
No patients/episodes	116/128
Rate per year (%)	1·22
No. patients taking NSAIDs	107
Rate per year (%)	1·58
Hospitalization rate while taking NSAIDs by ARAMIS Center (%)	
Santa Clara	1·16
Saskatoon	1·73
Phoenix	1·81
Stanford	1·66
Wichita	1·58
Relative risk for patients taking v not taking NSAIDs	5·2

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; ARAMIS, Arthritis, Rheumatism, and Aging Medical Information System.

*Years of observation, 9,525; years of NSAID therapy, 6,741.

tions relate to the USA population, with appropriate adjustments they should apply closely to all developed nations which use their drugs in a similar manner. On a national basis in the USA this translates to approximately 26,000 hospitalizations per year in RA patients. If estimates are extended to all patients taking NSAIDs with other diagnostic entities such as osteoarthritis there are nearly 80,000 NSAID-caused hospitalizations from all diagnoses each year in the USA.[5,6]

We turned next to the study of gastrointestinal deaths in rheumatoid arthritis (Table 2). Both our own data and the accumulated data in the literature suggested an excess of gastrointestinal deaths of approximately 3 per cent. Normally one expects to see 3 per cent of deaths categorized as gastrointestinal, in rheumatoid arthritis patients this number approximates to 6 per cent. Looking prospectively through our data we observed 17 gastrointestinal deaths, nearly all of which occurred in patients taking NSAIDs. The attributable gastrointestinal NSAID deaths represent approximately 1 in 1,000 per year, about 7 to 10 per cent of the hospitalization numbers. Overall, these numbers translate to 2,600 deaths annually in rheumatoid arthritis patients in the USA and nearly 8,000 deaths in all diseases. The Food and Drug Administration estimates are even

TABLE 2

Gastrointestinal deaths in rheumatoid arthritis

Prevalence	*Total deaths*	*GI observed*	*GI expected*	*GI excess*	*% Excess*
a. ARAMIS	251	15	8	7	2·78
b. 11 studies	1,863	96	45	51	2·74

Incidence calculations:

a. Using prevalence/21-year course = 2·75%/21 years = 0·13% deaths per year
b. Using hospitalization incidence/10 (estimated case fatality rate of 10%) = 1·10%/(year/10) = 0·11% deaths per year
c. Using prospective ARAMIS data = 17 deaths/9,525 years = 0·18% deaths per year

higher; that between 10 and 20,000 patients die each year in the USA from gastrointestinal events caused by NSAIDs.[5–8]

We looked next at risk factors, attempting to identify those patients who are at particularly high risk for gastrointestinal hemorrhage or other complications (Table 3). As others have indicated, age in years is the strongest single predictor of serious gastrointestinal events, either hospitalization or death. However, sex did not identify patients at higher risk. While most events occurred in women, most patients taking NSAIDs are also women, and the incidence of adverse events is nearly exactly the same in both sexes. Other variables that did increase risk included use of prednisone therapy, which even in doses averaging 6·9 mg per day was associated with a signficantly increased risk. Previous NSAID gastrointestinal side effects also identified those at greater risk, as did higher NSAID doses, and high disability levels.[5,6]

TABLE 3

Variables associated with gastrointestinal hospitalization or death in arthritis patients

Variable	*GI events (no. = 98)*	*No. GI events (no. = 1,596)*	*P value*
Female sex	76·5%	76·7%	0·97
Age (yr)	65·5	58·7	<0·001
GI symptoms reported with NSAID therapy	32·3%	18·6%	<0·001
Prednisone therapy	51·6%	31·0%	<0·001
Disease duration (yr)	18·8	16·9	0·11
NSAID dosage (% maximum PDR dosage)*	1·03	0·91	<0·05
Disability index (0–3)†	1·69	1·38	<0·001
Antacids or H_2-antagonist therapy	0·9%	19.2%	<0·001

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PDR, *Physicians' Desk Reference*.

*Maximum PDR dosage equals manufacturer's recommended dose.

†0, normal function; 3, totally disabled.

We developed several different risk factor models for identification of those at particular risk, using multiple regression equations and statistical techniques such as recursive partitioning. The simplest model for estimating risk in the individual is first to take 0·3 for each five years over the age of 50, second, add 1·2 if the patient is on prednisone, third add 1·4 if the patient has reported a prior NSAID gastrointestinal side effect and fourth add 0·5 if substantial disability is present. The sum of these four numbers represents the per cent risk of a substantial gastrointestinal adverse event in the next 12 months. Different patients range from nearly 0 risk to risks of 5 per cent or more. Patients at high risk, when exposed to NSAIDs for decades, are far more likely than not to have or have had a gastrointestinal event requiring hospitalization or resulting in death.[5,6]

Next, as an approach to reducing the population risk (Table 4) we sought to study the comparative toxicity of different anti-rheumatic drugs. This effort required a toxicity index which would enable us to make a quantitative comparison of drug effects, but unfortunately no such index had been described in the literature. In a long and difficult sequence therefore we began to identify the side effects to be accumulated into an index and which could be presented as an incidence rate of adverse reactions. The index was to be compiled from symptoms, laboratory abnormalities and hospitalizations related to drugs. Attribution

rules would be developed by which one could ascribe a hospitalization or death to a particular drug or drugs and the severity of a side effect as well as its presence would be recorded. Each of these would be summated into a crude toxicity index which would be adjusted using statistical methods for differences in the patient characteristics of those receiving different anti-rheumatic drugs.[9]

TABLE 4
Toxicity index scores and rankings

	All patients		
Drug	*No. of courses*	*Unadjusted toxicity index score (rank)*	*Standardized toxicity index score, ±SEM (rank)*
Aspirin	1,669	1·32 (1)	1·19±0·10 (1)
Salsalate	121	1·44 (2)	1·28±0·34 (2)
Ibuprofen	503	1·92 (3)	1·94±0·43 (3)
Naproxen	939	2·12 (4)	2·17±0·23 (4)
Sulindac	511	2·23 (5)	2·24±0·39 (5)
Piroxicam	790	2·53 (6)	2·52±0·23 (6)
Fenoprofen	161	2·68 (7)	2·95±0·77 (7)
Ketoprofen	190	3·63 (10)	3·45±1·07 (8)
Meclofenamate	157	4·13 (11)	3·86±0·66 (9)
Tolmetin	215	3·39 (8)	3·96±0·74 (10)
Indomethacin	386	3·59 (9)	3·99±0·58 (11)

Table 4 shows the crude and adjusted toxicity indices for patients receiving different NSAIDs. Both before and after adjustment, there are differences of three to four-fold between those agents which have the lowest toxicity scores and those which have the greatest toxicity. These substantial differences in toxicity are consistent across centers and are consistent with emerging data from other sources.[10] Meclofenamate, indomethacin, tolmetin and ketoprofen are most toxic; salsalate and ibuprofen are among the least. We do not have sufficient experience with some of the new agents to establish their place in this hierarchy.

Table 5 shows the relative toxicity of the NSAIDs and contrasts these with Toxicity Index scores for those patients taking disease-modifying anti-rheumatic drugs (DMARDs).[11] Of substantial clinical importance, the overlap in the toxicity between these two therapeutic classes are much more impressive than are their differences. Some agents which are considered disease-modifying, such as hydroxychloroquine, would be very non-toxic and the major DMARDs, such as methotrexate, are less toxic than the most toxic of the NSAIDs.

The old therapeutic approach to management of rhematoid arthritis, termed the 'therapeutic pyramid', was based upon the beliefs that rheumatoid arthritis was a benign disease, that NSAIDs were mild and benign agents, and that disease modifying anti-rheumatic drugs were too toxic for routine use. ARAMIS data, consistently and reproducibly demonstrating that rheumatoid arthritis is a severe disease resulting in major disability and frequent premature death, that NSAIDs are more toxic than expected, and that the disease-modifying drugs, with the potential to improve long-term outcomes, are less toxic than expected, have contributed strongly to contemporary efforts to 'invert the pyramid' and to manage rheumatoid arthritis more aggressively with disease-modifying drugs employed early in the course and consistently thereafter.[7–11]

TABLE 5
Comparative toxicity of 6 DMARDS and 10 NSAIDS*

Rank	*DMARD*	*Standardized toxicity index, mean±SEM*	*NSAID*	*Standardized toxicity index, mean±SEM*
1			Salsalate	1·28±0·34
2	Hydroxychloroquine	1·38±0·15		
3			Ibuprofen	1·94±0·43
4			Naproxen	2·17±0·23
5			Sulindac	2·24±0·39
6	Intramuscular gold	2·27±0·17		
7			Piroxicam	2·52±0·23
8			Fenoprofen	2·95±0·77
9	Penicillamine	3·38±0·36		
10			Ketoprofen	3·45±0·74
11	Methotrexate	3·82±0·35		
12			Meclofenamate	3·86±0·66
13	Azathioprine	3·92±0·39		
14			Tolmetin	3·96±0·74
15			Indomethacin	3·99±0·58
16	Auranofin	5·25±0·32		

*DMARDS = disease-modifying antirheumatic drugs; NSAIDS = nonsteroidal anti-inflammatory drugs.

Table 6, presenting our most recent data, contrasts the overall toxicity index of different NSAIDs with a gastrointestinal toxicity index, in which only those scores arising from gastrointestinal side effects are included in the index. The similarity between the rankings is obvious, and one can also document by these comparisons the dominant contribution of gastrointestinal toxicity to the total toxicity experienced with these agents.

A final observation from these studies has to do with the special role of aspirin, the oldest and perhaps the most maligned of this drug class. NSAIDs were developed and tested against aspirin in randomized control trials for each drug, repeatedly demonstrating that the proposed agent was as effective as aspirin and less toxic. On this basis, these drugs were approved for general use.

TABLE 6
Gastrointestinal (GI) and total toxicity index scores

	Number of courses	*Years at risk*	*GI toxicity index*	*Total toxicity index mean (SE)*
Aspirin	1,516	3,056	1·06 (0·16)	1·77 (0·20)
Salsalate	187	241	0·87 (0·24)	2·00 (0·46)
Ibuprofen	577	826	1·16 (0·17)	2·68 (0·44)
Naproxen	1,062	1,801	1·78 (0·25)	3·01 (0·31)
Sulindac	562	860	1·63 (0·24)	3·92 (0·78)
Piroxicam	814	1,167	2·07 (0·24)	3·97 (0·32)
Tolmetin	243	306	2·16 (0·50)	4·13 (0·62)
Fenoprofen	158	221	2·48 (0·63)	4·25 (0·78)
Diclofenac	415	337	2·17 (0·38)	4·48 (0·56)
Ketoprofen	259	253	3·09 (0·54)	4·69 (0·70)
Indomethacin	418	613	2·40 (0·42)	5·15 (0·62)
Meclofenamate	165	179	4·03 (0·78)	5·94 (0·92)

When, however, we looked at the actual toxicity experienced with these

drugs, we found, surprisingly, that aspirin was among the least toxic of the NSAIDs.[9,10] Accordingly, in detailed study[12] we sought to explain this contradiction. It could not be explained by reporting bias or by patient selection. It could be explained in part by the use of enteric-coated aspirin preparations in clinical practice as compared with the plain aspirin used in the trials. The most important effect, however, came from differences in dose. In the published clinical trials the aspirin doses ranged from 4,000 to 4,800 mg per day. In practice, however, we found the average dose to be only 2,665 mg per day. In contrast, in naproxen clinical trials the dose was 500 mg per day while in actual practice the naproxen dose is more than 750 mg per day. Thus, under the conditions of the controlled trials aspirin would appear more toxic than NSAIDs but under the conditions of clinical practice, aspirin is a relatively non-toxic NSAID and requires re-evaluation of its clinical role.[12]

Clearly, we have neglected the concerns of Oliver Wendell Holmes in our use of NSAID therapy over the past three decades. We have used these drugs more frequently, have pushed the doses used progressively higher, and have prescribed more fequently to older individuals who have the highest risk. Clearly, a result has been that some individuals are placed at greater risk than justified by likely benefit. I believe that it is difficult to make a case for the use of these medications at anti-inflammatory doses in very many patients.

Osteoarthritis, the American term, is usually more appropriately termed 'osteoarthrosis' on this side of the Atlantic. The distinction is important. The non-inflammatory loss of articular cartilage, with consequent bony reaction, represents the underlying pathophysiology. What inflammation is present most likely represents in large part a defense mechanism to remove damaged tissues. Yet we often treat patients with anti-inflammatory doses of medications with the goal of managing pain. As a result, many are hospitalized, and some die.

Recent studies[21,22] document that simple analgesics can be as effective as NSAIDs in osteoarthrosis, and that lower analgesic doses of NSAIDs are as effective as higher doses. Others[23,24] have been concerned that anti-inflammatory doses may be associated with accelerated development of cartilage destruction. What is the case for high-dose NSAID therapy?

Moreover, with revised therapeutic strategies in rheumatoid arthritis emphasizing early and continuous use of disease modifying anti-rheumatic drugs which are more able to reduce inflammation substantially, the role of the NSAID in RA may be challenged. Thus, since all patients with active inflammation will be on a DMARD, one may not wish to employ the anti-inflammatory actions of NSAIDs since this effect may be better achieved with the DMARDs. Hence, the coming role for use of NSAIDs as optional adjuncts to therapy, in analgesic doses only, with a potential benefit of lessened toxicity from these agents.[12–15]

These studies of the toxicity of anti-rheumatic drugs have been exciting and important. Toxicity from these agents appears to exceed that of toxicity from any other class of medications.[16–20] A variety of approaches to minimizing this problem are available. These include use of lower analgesic doses of these medications, substitution of acetaminophen (paracetamol) when clinically possible, use of the least toxic NSAIDs, their careful use in older, high risk patients and use of co-therapy with prostaglandin analogs in those few high risk patients who definitely require NSAID treatment. The classical epidemiologic sequence is identification of a problem, quantitation of its magnitude, development of strategies to ameliorate the problem, and implementation of these strategies. NSAID gastropathy is currently passing through this sequence.

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