OLD DRUGS – OLD PEOPLE – NEW INSIGHTS

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ABSTRACT

Dr. Dan Sitar was the recipient of the 2004 CSCP Senior Investigator Award at the First Canadian Therapeutics Congress held in June 2004. He presented a lecture highlighting some of the studies he participated in that have contributed to an increased understanding of the role of aging on drug disposition and effect.

Key Words: Aging; drug disposition; CSCP Senior Investigator Award

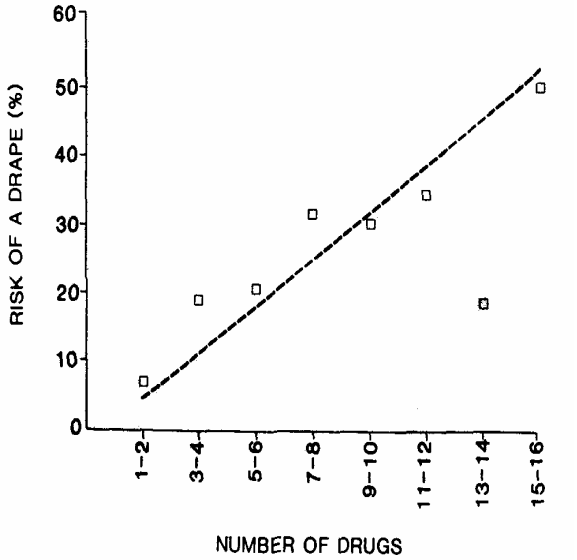
Much of the research that conforms to the dictate of the title of this presentation is encompassed by the following question, "Is age itself an important underlying contributor to altered drug disposition and effect?"

A justification for this focus is related to the observation that we are being confronted by a growing number of elderly patients, who, because of their accumulating chronic diseases, are most often prescribed drug therapy as a means to improve their quality of life. In pivotal studies from the University of Manitoba, we found, like many before us, that the elderly were disproportionate users of drugs as therapy[1] they often appeared at the Emergency Department with significant morbidities; and they were admitted to hospital for management of acute exacerbations.[2] We confirmed the observation that, upon admission to hospital, the risk of a drug-related adverse patient event (DRAPE) was clearly related to the number of prescribed drugs (Figure 1).

Our insight to this observation was to place a denominator on the phenomenon, and to demonstrate that age itself was not the primary mechanism for putting the patient at risk of a DRAPE (Figure 2).[2] However, this analysis did not rule out the possibility that there might be differences in the disposition, efficacy and toxicity of drugs as a function of age, and we concurrently examined the potential role for age as a confounding factor in the optimization of drug therapy for individual patients.

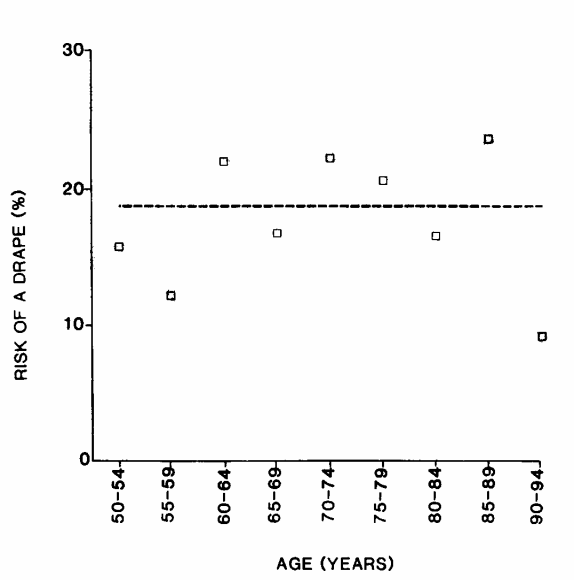
The following presentation is a summary of some of our studies that have contributed to an increased understanding of the role of aging on drug disposition and effect.

Figure 1 Relationship of DRAPE risk to the number of prescribed drugs ($r = 0.77$; $P < 0.001$).



(Reproduced with permission from Blackwell Publishing. Drug-associated hospital admissions in older medical patients. Figure 2&3, Grymonpre RE, et al, *J Amer Geriartr Soc* 1988 36:1092-1098)

Figure 2 Relationship between DRAPE risk at admission and age.



Dashed line shows mean rate of 19% of all 863 eligible admissions (Reproduced with permission from Blackwell Publishing. Drug associated hospital admissions in older medical patients. Figure 2&3, Grymonpre RE, et al, *J Amer Geriartr Soc* 1988 36:1092-1098)

Propylthiouracil

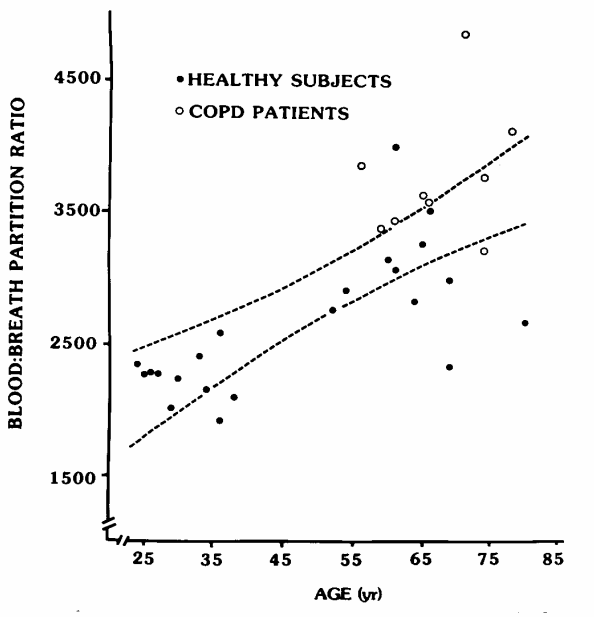
While at the University of Minnesota in the early 1970s, I was the first to report a high performance liquid chromatographic assay for propylthiouracil, and a representative drug concentration versus time profile in healthy human volunteers.[3] We conducted studies in young and elderly hyperthyroid and hypothyroid patients. There were trends to increased apparent volume of distribution and plasma half-life for PTU as a function of age. Our insights included that propylthiouracil has a very short half-life, about one hour; its disposition is affected by thyroid status; and a pharmacokinetic basis was established for a more rational dose regimen in patients.[3,4]

Theophylline

I would be remiss if I didn't spend a few moments on the drug that undoubtedly helped to establish my laboratory as a significant contributor to the principles of clinical pharmacology. In the early 1970s, just after my arrival at McGill University, I developed a high performance liquid chromatographic assay for theophylline.[5]

We went on to complete several studies on theophylline disposition in various patient populations. The key findings from this work include that pharmacokinetic principles were developed to increase the safety of theophylline in patient populations, and the demonstration that even drugs with low hepatic extraction ratios can have substantial impairment of their disposition in cardiovascular and hepatic diseases.[6]

Figure 3 Comparison of blood: breath partition coefficients with age.



The dashed lines represent 95% confidence intervals for the correlation. (Reproduced with permission from Lippincott Williams &Wilkins. Effect of age and chronic obstructive pulmonary disease on the Breathalyzer estimation of blood alcohol level. Fig. 1, Wilson et al, *Alcoholism Clin Exp Res* 1987 11(5):440-3)

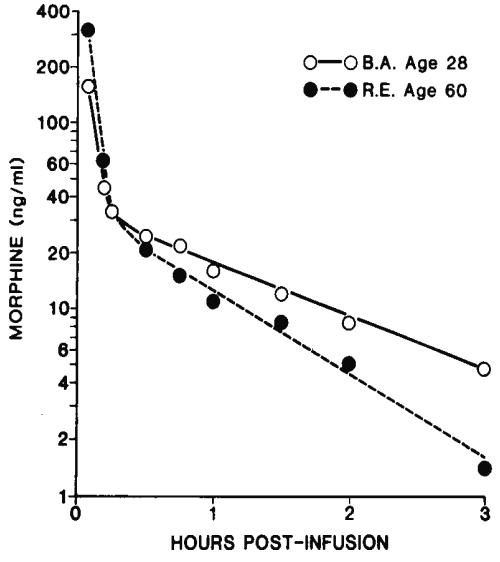
Alcohol

Although our laboratory was privileged to undertake several important studies concerning the clinical pharmacology of alcohol, the focus of today's presentation relates to a study in which we attempted to relate aging and lung disease to the ability of breath analysis to accurately predict blood alcohol concentrations. A summary of the findings of this study is presented in Figure 3. To our surprise, even healthy elderly persons with normal pulmonary function parameters, who consumed alcohol in a controlled environment, produced

breath samples that considerably underestimated their true blood alcohol concentration. Although lung disease increased the discrepancy between direct blood alcohol determination and breath analysis, it had a much lesser role than would have been expected in the face of the changed excretion of alcohol in the breath of older healthy volunteers.[7].

This finding has implications for the interpretation of end tidal volatile anesthetic concentrations in elderly surgical patients, and brings into question whether the belief that the elderly are more deeply anesthetized for the same end tidal anesthetic concentration truly reflects the blood concentration that is perfusing the brain. The key findings of this study include that the Breathalyzer is a flawed approach for the estimation of blood alcohol concentration, and that the use of end tidal anesthetic concentration as a measure of anesthetic depth may be misleading.

Figure 4 Plasma morphine concentration-time curves for an elderly and a young individual representative of each group



Morphine concentrations are expressed as nanograms of morphine base per millilitre of plasma.

(Fig 1&2 upper panel reproduced with permission from the American Society for Clinical Pharmacology & Therapeutics. Age related morphine kinetics. Owen JA et al, *Clin Pharmacol Ther* 1983 34:364-8).

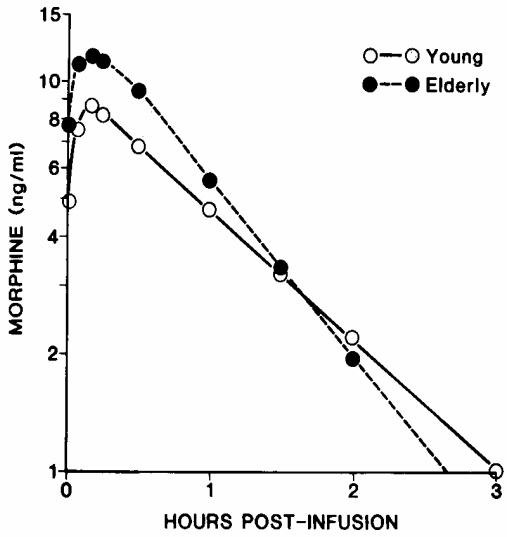
Morphine and Selected Synthetic Opiates

Our laboratory developed a high performance liquid chromatographic assay for morphine[8], and used it to determine the possibility of age and sex-associated difference in morphine disposition, and by inference efficacy and toxicity (Figures 4 and 5).[9]

The key findings included the fact that the beta disposition phase for morphine in healthy elderly persons was more rapid than in healthy young individuals after an equivalent intravenous mg/kg dose. Modeling of the data also suggested that higher concentrations of morphine occurred in the brain (peripheral kinetic compartment) in older persons. These data provided pharmacokinetic support for the clinical observations of increased sensitivity of elderly persons to morphine.

It was left to others subsequently to demonstrate the important role of morphine-6-glucuronide in the maintenance of analgesic response after a dose of morphine, an important finding to reconcile our observation of a more rapid beta disposition phase for the parent drug in older patients.

Figure 5 Peripheral compartment morphine concentration-time curves calculated from the mean kinetic constants for the elderly and young groups.



(Fig 1&2 upper panel reproduced with permission from the American Society for Clinical Pharmacology & Therapeutics. Age related morphine kinetics. Owen JA et al, *Clin Pharmacol Ther* 1983 34:364-8).

TABLE 1 Comparative pharmacokinetic disposition as a function of age for the opioid drugs morphine, fentanyl and alfentanil.[9-11]

	Morphine	Fentanyl	Alfentanil
Vd_{ss}	↓	↑	↔
Beta $t_{1/2}$	↓	↑	↑
Cl_p	↓	↑	↓

Subsequently, we were fortunate to have been able to repeat the morphine protocol with other synthetic opioids developed for clinical use .[10,11] The key findings from a combination of our studies with morphine, fentanyl and alfentanil are presented in Table 1. The major lesson was that knowledge concerning age effects on the disposition of morphine could not automatically be extrapolated to optimization of the clinical use of other opioid drugs.

Amantadine

I began to work with amantadine when Dr. Aoki returned to McGill University after completing some work on influenza research in the United Kingdom. He convinced me that this was a fruitful area for clinical pharmacology research, and we went on to complete several studies that provided the basis for optimization of its use in elderly patients.[12] We demonstrated that renal function was the limiting factor that controlled its disposition, and that the elderly were likely to experience increased toxicity if the dose developed for the treatment of younger patients was indiscriminately applied to the elderly patient.[13,14] Our most recent extension of this aspect of our studies on amantadine was the demonstration that use of serum creatinine to adjust the amantadine doses in elderly institutionalized patients resulted in lower amantadine doses, maintained efficacy, and reduced toxicity.[15] Due to early observations that amantadine was secreted by the kidney, we designed a study to determine whether there were age and/or sex differences in amantadine elimination in humans. To our surprise, we found that women had a reduced renal clearance of amantadine compared to their male counterparts (by about 40%), and that the greater renal clearance in men could be suppressed by concurrent administration of quinine or quinidine; however, concurrent administration of quinine or quinidine was without effect on the renal clearance of amantadine by women.[16,17] This observation stimulated a series of laboratory investigations related to the mechanisms by which amantadine renal tubular transport was controlled .

As a result of a short publication indicating that a minor portion of an administered dose of amantadine was acetylated, we went on to determine the mechanism by which this metabolic conversion was mediated. To our surprise, neither NAT1 nor NAT2 could account for acetylation of amantadine. Subsequent studies with transgenic mice and subcellular fractions from mouse liver demonstrated that the responsible enzyme was in fact spermine/spermidine N^1-acetyltansferase (SSAT-1), and that amantadine was a specific substrate for this acetyltransferase enzyme.[12] This discovery is protected by a patent, and has led to our current studies to determine whether amantadine may serve as a diagnostic test for cancer, since SSAT-1 is upregulated in tumor tissue.

CONCLUSION

Our findings described briefly above provide considerable support to the hypothesis that aging alters drug disposition and efficacy. Therefore, it is important to continue this research in order to understand more clearly how these age-associated changes in drug disposition may be applied to the further individualization of drug therapy. The clinical consequences of these changes, relative to the added effects of disease, offer many opportunities for further research, and optimistically to the improved quality of life of the elderly.

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