Dose response relationships in clinical pharmacology
L Lasagna, S Erill, C A Naranjo, editors

THE RELATION BETWEEN DOSE AND RESPONSE TO DIAGNOSTIC DRUGS

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A drug is "any chemical compound that may be used on or administered to humans or animals as an aid in the diagnosis, treatment or prevention of disease ..." (1). Correct diagnosis is the first step in rational therapy and a number of compounds owe their clinical usefulness, entirely or in part, to their ability to aid in diagnosis. The ratio, efficacy/toxicity, is as important for diagnostic as for therapeutic drugs, but the efficacy of a diagnostic drug is measured by such criteria as the sensitivity, specificity and overall accuracy of the test in which it is used. In order to judge the accuracy of any new diagnostic test one needs a separate, fully reliable way to establish the diagnosis (a "gold standard"), which may require invasive procedures or prolonged clinical observation and thus make a comparison of several different doses of a diagnostic drug a formidable undertaking. The fact that many diagnostic tests simply give a yes-no answer may also lessen interest in exploring a wide range of doses of a diagnostic drug; an alternate strategy in developing such tests is to choose one dose that regularly exerts a measurable effect on the parameter of interest, e.g. blood pressure or blood glucose concentration, and then determine what degree of response, e.g. change in blood pressure or blood glucose concentration, represents the best demarcation point between normal and abnormal. Finally, many individuals receiving a diagnostic drug will prove in the end to have no disease at all. This fact makes signficant toxicity even more undesirable for diagnostic than for therapeutic drugs and greatly limits human dose-response studies of diagnostic drugs that have significant toxicity, e.g. roentgenographic contrast media. Therefore it is not surprising that human dose-response data for diagnostic drugs are somewhat fragmentary. This situation is regrettable, for the dose-response relationships of these drugs raise several interesting questions and considerations.

General Considerations

The chief classes of diagnostic drugs are shown in Table 1. Classifications based on indications for use are rational but often, as here, they group together drugs that are heterogenous in chemical structures and even in biochemical or physiological effects. Thus pentagastrin, an agonist for gastric acid secretion, is grouped with edrophonium, an enzyme inhibitor, as the latter's use in the diagnosis of myasthenia gravis depends on its ability to increase muscle

TABLE 1

DIAGNOSTIC (INFORMATIONAL) DRUGS

CLASS	EXAMPLES	USE		
		TO SUPPORT THE DIAGNOSIS OF:	TO DETERMINE:	TO AID IN IMAGING OF:
1. Antigens	Benzylpenicilloyl polylysine (PPL)*	Allergy to penicillin G		
	Tuberculin purified protein derivative (PPD)	M. Tuberculosis infection**		
2. Markers (tracers) to measure a function or compartment without altering it	Indocyanine Green		Cardiac output	
	Technetium Tc-99m labeled human serum albumin		Plasma volume	
3. Stimulating or inhibiting drugs				
a. Stimulating	Pentagastrin		Gastric acid-secreting ability	
	Edrophonium (Tensilon)***	Myasthenia gravis		
b. Inhibiting	Dexamethasone	Cushing's syndrome		
	Saralasin	High-renin hypertension		
4. Drugs used with Imaging Procedures				
a. Roentgenographic contrast media	Iodipamide meglumine (Cholografin)			Bile ducts and gall bladder
b. Radiopharmaceuticals for scintigraphy	Sodium Pertechnetate Tc-99m			Thyroid gland Salivary gland
c. Magnetic Resonance Imaging (MRI) contrast agents	Gadolinium diethylene-triaminepentaacetate meglumine (gadopentetate meglumine; Gd DTPA)			Kidney Brain tumors

*PPL is able to elicit a reaction in sensitized individuals but is itself a poor antigen for sensitizing.
**A positive test does not necessarily indicate active infection.
***See text.

strength. There is some overlap among the classes in Table 1 but we have found the classification useful despite its imperfections. As compounds such as indocyanine green provide information which may at times be useful in diagnosis but more often serves other purposes, a better term than diagnostic drug would perhaps be informational drug but we will use the more established term in this discussion.

A fundamental therapeutic strategy is to select, if possible, a dose very high on the dose-response curve for therapeutic effect and very low on the curve(s) for adverse effect(s) Mutatis mutandis, this strategy also applies to diagnostic drugs. It has been successfully achieved for many compounds in Class 2 above, i.e. desired information can be obtained with little risk, and Class 2 will not be discussed further here. For Class 4a, especially those compounds administered intravascularly, the incidence of adverse effects from doses that allow adequate visualization is not negligible (2,3,4) There is understandable reluctance to submit individuals to a wide range of doses of contrast media in order to explore the relation between dose and adverse response, but a relatively narrow dose range was explored by Eldridge et al (5) These authors reviewed records of 120 patients who had undergone i.v. injections of contrast media for angiography. Fifty-two received a 70% iodopyracet (Diodrast) solution, 44 received 75% sodium iodomethamate (Neo-iopax) and 24 received a third iodinated compound, 70% Urokon, respectively. In each group, one subgroup received a low dose ($\leq$0 9ml/kg), another received an intermediate dose (1.0-1 9ml/kg), while a third received a high dose (2.0-3.6ml/kg) The incidence of significant reactions after iodopyracet was 18%, 59% and 61% for the low, intermediate and high doses respectively. Though data analysis was not given in the paper, our analysis shows a significant ($p=0.015$) difference between the incidence of reactions with the low dose and the incidence with the two other doses combined. The respective incidence at the 3 dose levels of sodium iodomethamate was 25%, 36% and 37% (n.s.) and of Urokon, 0%, 0% and 20%(n.s.). Comparing drugs rather than doses, the overall incidence of reactions with iodopyracet was clearly higher than with Urokon; the difference between iodopyracet and sodium iodomethamate was of borderline significance ($p=0.078$) These results suggest that the dose-response curve for iodopyracet is steeper than the curve for iodomethamate. Subsequent exploration of still higher doses of the latter would have been interesting but, for ethical reasons, inappropriate Even with Urokon, where the only adverse reaction was in one of the 5 patients receiving the high dose, study of still higher doses would have been inadvisable since that one patient's reaction was fatal. Ansell et al (4) found a probable relation between

dose and serious adverse effects in i.v. urography

Although the finding that large doses of contrast media produce more contrast than small doses is certainly no surprise, data on the magnitude on the effect are of interest. Perkerson et al (6) reported the quantified (Hounsfield units) densities of hepatic CT images in 60 patients 1 min after injection of a diatrizoate meglumine solution. Three subgroups of twenty patients each received 50, 100 and 200 ml i.v., respectively. Calculations from the authors' data show that the 3 doses caused respective increases of 27.5, 46.2 and 76.1% over pre-injection densities. Some indication of the time-action curve was given by the results of re-imaging 4 h later, when the respective increases over pre-injection value were 14.3, 23.9 and 40.7%. However, the most important relation is not between dose and density of image but between dose and accuracy of diagnosis. A discussion of the latter is beyond the scope of this paper but involves such important additional factors as fidelity of the image (modulation transfer function [MTF]) and the effect of the radiologist's decision criteria on the probability of under - or overdiagnosis, a problem that can be studied by receiver operating characteristic (ROC) analysis. The fundamental problem here - difficulty of translating quantitative data on a limited effect into overall clinical results - exists for both diagnostic and therapeutic drugs, e.g. the relation between the acute dose of an antihypertensive drug and drop in blood pressure is not necessarily the same as the relation between the dose given regularly and survival time of hypertensive patients, owing to many intervening factors. But the types of intervening factor are very different for diagnostic than for therapeutic drugs.

Special Considerations Although the general considerations noted above also apply to the other classes in Table 1, each of these other classes has peculiarities that merit attention. The remainder of this paper will be concerned with these individual questions and considerations.

Class 1. A recurrent question about the dose-response relationship for antigens is whether there is any graded response at all. The relation between dose of antigen and ability to sensitize is not under discussion here, but rather the relation between eliciting dose and response in an already sensitized individual. Is the response to challenge by antigen simply all-or-none, or is it graded? Early studies in dogs (7) and man (8) suggested an all-or-none response. But Carr and Currie (9) showed, in guinea pigs sensitized passively (to decrease individual variation) to egg albumin, that a graded bronchoconstrictor response to increasing doses of antigen did occur (Fig. 1)

The most convincing evidence for a graded response in man comes not from results

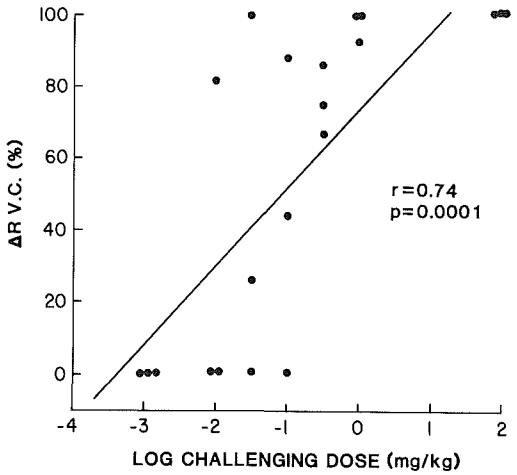

Fig. 1 Bronchoconstrictor response, expressed as R.V.C. (ratio, tidal volume/ intrapleural pressure change), to i.v. antigen in sensitized guinea pigs. Each dot represents a separate animal. Adapted from "Comparative effects of compound 48/80, histamine and antigen, and the relation between challengine dose of antigen and anaphylactic response in guinea pigs sensitized to egg albumin" (Ref 9). By permission of S. Karger AG, Basel.

of skin testing but from reports, spanning three decades, of the deliberate hyposensitization of patients allergic to penicillin (10,11). In this procedure increasing doses of penicillin are administered, usually at short intervals, to a patient known to be allergic to the drug; if a significant reaction occurs after a given dose, that same dose is usually repeated until the patient tolerates it without reaction, then the rising dose schedule continues. Despite the gradual hyposensitization, higher doses often elicit reactions that are clearly more intense than those observed after lower doses, e.g. edema of eyelids after 1 2 mg (2,000 u.) penicillin i.m., intense burning and swelling of the lids when the ascending dose reached 12 mg, and edema, erythema and itching at several additional sites, plus systemic symptoms, when the dose reached 150 mg (10). Similar results have been reported with intradermal injection of rising doses (11).

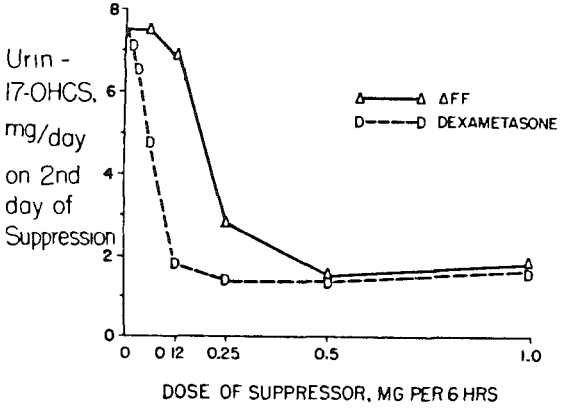

Fig. 2 Suppressive effect of dexamethasone and "ΔFF" (see text) on urinary 17-hydroxycorticoid excretion in normal humans. From G.L. Liddle: "Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome" (Ref 15). By permission of the Endocrine Society, Bethesda, and Williams and Wilkins, Baltimore.

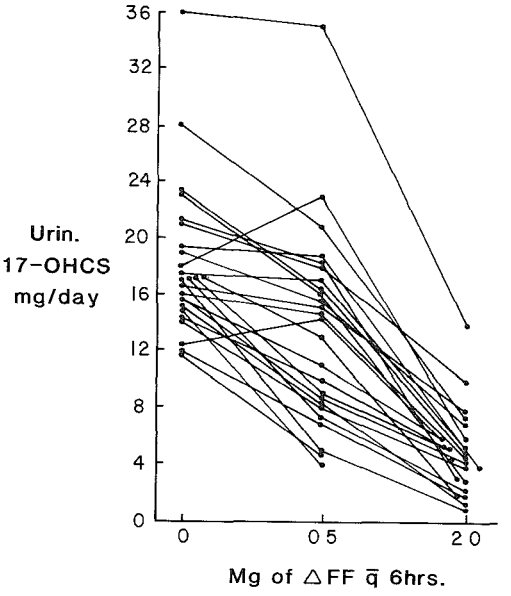

Fig. 3 Suppressive effective of dexamethasone and "ΔFF" (see text) on urinary 17-hydroxycorticoid excretion in patients with bilateral adrenocortical hyperplasia. Same source as Fig. 2.

Although such reports usually describe only a single patient, the risk of the procedure forces close, constant observation by a physician, with careful attention to details of dose and effect. Thus the published reports have a high degree of reliability. We conclude there is evidence that at least some allergic individuals show a graded response to antigen. However, systemic administration of any dose of antigen to an allergic patient remains risky, for neither the lowest dose that will have significant effect nor the slope of the dose-response curve is predictable for a given patient. Indeed, even skin testing for penicillin allergy, which has a good safety record in thousands of patients (12), is not completely benign; one patient died quickly after a scratch test with about 300 ng (13).

Class 3. Whether these drugs produce responses requiring chemical measurements, e.g. pentagastrin and dexamethasone, or cause more overt physiological responses, e.g. edrophonium and saralasin, the responses can be graded with varying degrees of precision. There is thus the possibility that the test may not only distinguish between normal and abnormal but may also, in case of an abnormal response, provide information on the nature of the abnormality via the degree of abnormal response. The dexamethasone suppression test, thanks to the fine work of Liddle (14,15), is a classical example of such use of a dose-response curve. Using urinary 17-hydroxycorticosteroids (17-OHCS) as a measure of glucocorticoid secretion, he studied the effect of different doses of dexamethasone and of a demethylated analog "ΔFF" in suppressing this secretion (Fig. 2). He then showed that 0.5 mg of either compound every 6 h suppressed urinary 17-OHCS below 2.5 mg/24 h on the second test day in normals. Each of 24 fully tested patients who were subsequently proven, by other means, to have bilateral adrenocortical hyperplasia resisted suppression to normal levels by the 0.5 mg dose but did show further suppression after 2 mg every 6 h (Fig. 3). Seven patients with subsequently proven cortical neoplasms showed no suppression after either dose. The test remains useful to this day.

Work from the more distant past throws a curious sidelight on one aspect of this question. A century ago the conflict between homeopathy and allopathy aroused interest in dosimetry. A paper from that era, cited in a more modern review (16), contained a suggestion by the "dosimetrists" that differences in dose might cause not only quantitative but even qualitative differences in response, e.g. might convert a sedative drug into a stimulant. In modern therapy myasthenic patients treated with a long-acting cholinesterase inhibitor are weak if underdosed, have improved strength when given a dose in the proper (individual) range but again become weak, owing to excessive depolarization of

the motor end-plate, if overdosed. The diagnostic drug, edrophonium, aids in distinguishing between underdosing and overdosing, as edrophonium improves muscle strength in the former situation and fails to relieve, or even increases weakness in the latter.

Class 4b. Among drugs that currently have wide, established clinical use no other group, diagnostic or therapeutic, is regularly administered systemically in such small doses as are radiopharmaceuticals. A dose of 2 mCi (74 MBq) ^{201}Tl, given as TlCl for myocardial scintigraphy, contains approximately 9 4 ng ^{201}Tl, plus $\leq$0.2 ng contaminating ^{202}Tl or about 11.3 ng thallium chloride. A dose of 3 mCi (111 MBq) ^{99m}Tc, given as $NaTcO_4$ for thyroid imaging, contains approximately 570 pg ^{99m}Tc. Additional Tc is present because ^{99m}Tc decays, with a half-life of 6 h, to ^{99}Tc, which has a half-life of 2 2 x 10^5 years. The total Tc content varies, depending on the elapsed time between elution from the generator and injection into the patient, but a reasonable value for 3 mCi (111MBq) is about 4 ng total Tc, or 7.5 ng (40 pmol) $NaTcO_4$ injected.

The desired response to radiopharmaceuticals is selective uptake by the target organ or lesion. Our ability to detect in vivo localization of such minute quantities is due to the exquisite sensitivity of modern instruments for detecting gamma and x-rays. A consideration implicit in all diagnostic studies utilizing any type of recording instrument - dependence of the test's accuracy on the performance of the recording instrument - becomes explicit in scintigraphy and other imaging modalities. Whereas roentgenography and MRI use contrast agents only for certain studies, scintigraphy regularly requires administration of a radiopharmaceutical. One of the simplest and most fundamental "dose-response" relationships in scintigraphy is the count rate response of the gamma camera to various amounts of a radionuclide presented to its field of view To test camera linearity we used a Siemens ZLC gamma camera with an all-purpose collimator to image a thyroid phantom containing 8 different amounts of ^{99m}Tc, ranging from 8 μCi (296 mBq) to 5.9 mCi (218.3 MBq) and recorded mean and maximum counts · pixel $^{-1}$ · min $^{-1}$ in the scintigraphic region of interest. Each amount was imaged once but the images were obtained in random order at various times over a 2 d period. Camera linearity was excellent ($r > 0$ 99 for both mean and maximum counts plotted against amount of ^{99m}Tc).

Using the same camera we studied thyroidal uptake of the [^{99m}Tc] pertechnetate ion, using 5 doses ranging from 47 μCi (1.74 MBq) to 3 mCi (111 MBq), in a normal man. Imaging began 20 min after i.v. injection of each dose.

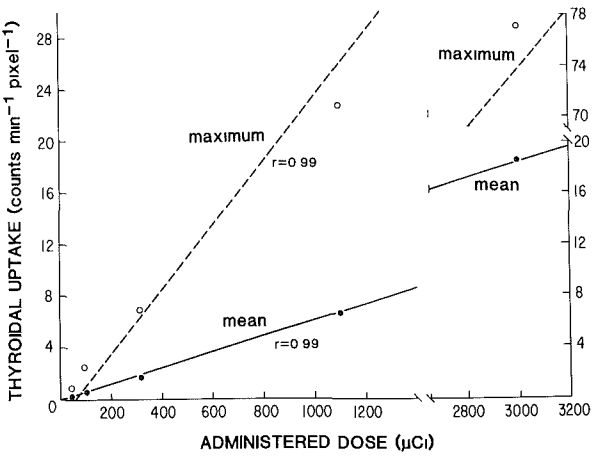

Fig. 4 Relation of administered dose of (^{99m}Tc) NaTcO4 to thyroidal radioactivity in a euthyroid man.

The mean and maximum counts · pixel^{-1} · min^{-1} are shown in Fig. 4. As the response we measured was uptake, which depends on an active transport system (presumably the same as that which transports the iodide ion) rather than receptor binding, the linearity of the curve (r=0.99 for both mean and maximum counts) is perhaps not surprising. But the usual dose for thyroid imaging is 1-10 mCi (37-370 MBq) and the maintenance of a linear dose-response relationship with doses well below this range suggests that no pertechnetate "sticks" to the carrier transporting the anion, even when the entire gland is presented with only femtomol amounts.

Despite their physiologic interest these data do not, of course, provide information on two previously mentioned factors bearing on the diagnostic accuracy of imaging modalities, MTF and decision-making by the observer.

Class 4c. A comparison of MRI with scintigraphy from a pharmacologist's standpoint has been published elsewhere (17). MRI is much less sensitive than scintigraphy and requires doses of contrast agents that are usually in the range of several grams. Whereas radionuclides produce a signal via their own emission, the most important group of MRI contrast agents currently under clinical

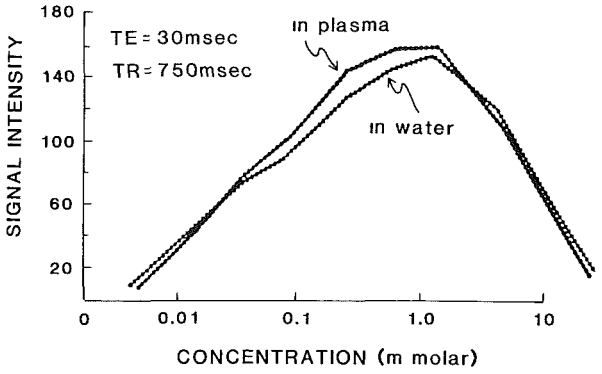

Fig. 5 Contrast enhancement in vitro with Gd DTPA at 1.5 tesla. From V.M. Runge et al: "The field strength dependence of contrast enhancement with gadolinium DPTA in MRI" (Ref 18). By permission of the Society of Magnetic Resonance in Medicine, Berkeley.

investigation utilizes paramagnetic elements such as gadolinium and manganese, which do not produce a signal by their own resonance but exert their effect on signal intensity (SI) indirectly by shortening relaxation times of protons already present in the tissue. The relation between concentration of a contrast agent and changes in SI is complex (18) (Fig. 5).

Many potential MRI agents have been studied, and pioneering work by European investigators has been especially notable, but at present the only agent approved for clinical use by the U.S. Food and Drug Administration is Gd DTPA (see Table 1) developed by Weinmann and co-workers (19,20). In man an i.v. dose of 0.005 mmol/kg did not increase renal SI but doses of 0.05, 0.1 and 0.25 mmol/kg all caused satisfactory and approximately equal increases in SI (21). A pharmacokinetic comparison of 0.1 and 0.25 mM/kg in man has been published (22) but the former dose has been widely adapted for clinical use and at present we must depend chiefly on animal studies for further data on the relation of dose to changes in relaxation times and SI. The acute i.v. LD_{50} of Gd DPTA is 5-12.5 and 10-15 mmol/kg in mice and rats, respectively (23). As Gd DPTA appears both clinically useful and safe at the currently accepted dose, further exploration of its dose-response curve in man is unlikely. If agents with still greater margins

of safety are developed, a wider exploration of their dose-response curves may be both practical and desirable.

But which response should we measure? The primary purpose of contrast agents is to enhance contrast by selective changes in intensity. But relaxation times provide important diagnostic information about various tissues and therefore the effect of contrast agents on relaxation times may be of interest per se, quite apart from the changes in SI and contrast that result from these changes in relaxation times. As the SI-increasing effect of Gd is primarily related to shortening of T1, the studies of Fiel et al (24) are of interest. They studied the effect of various doses of a Mn-containing porphyrin, "Mn (III)$TPPS_4$", in tumor-bearing mice. The relation between administered dose and concentration of the agent in various tissues is shown in Fig. 6. The relation between dose and T1 relaxation times of these tissues is shown in Fig. 7. Although much of the selectivity of MRI contrast agents, like that of radiopharmaceuticals, depends on selective concentration in tissues of interest, the relation between concentration and changes in relaxation times may also differ among tissues. Bousquet et al (25) showed, in rats receiving Gd tetra-azocyclododecane tetraacetic acid, that equivalent tissue concentrations of Gd increased the relaxation rate (1/T1) of liver more than spleen, and of spleen more than blood.

As noted above, diagnostic drugs permit construction of time-action curves as well as dose-response curves. In a rat heterotopic cardiac transplant model we found that Gd DTPA increased the intensity of the graft image, the increase being signficantly ($p<0.01$) greater in rejecting allografts than in non-rejecting isografts. The ratio of intensity at various times after injection (I_t) to pre-injection intensity (Io) is shown in Fig. 8. Although the ratio, I_t/Io, was by definition 0 at time 0 in our study, intensity itself and relaxation times are, of course, not 0 at time 0 in time-action studies with MRI contrast agents and are not 0 at dose 0 in dose-response studies. As MRI is feasible even without contrast agents, image intensity and relaxation times are measurable before injection of contrast agents. Despite the importance of T1 changes in mediating the effect of Gd on intensity, we found a significant ($p<0.05$) correlation between I_t/Io following Gd DPTA and the pre-injection T2, but not between I_t/Io and pre-injection T1. We believe the correlation with T2 is based on the pathophysiology, i.e. increased vascular permeability and edema. Thus the enhancing effect of the agent is via T1 changes. but a better predictor of the abnormal state that allowed the contrast agent to enter rejecting hearts more

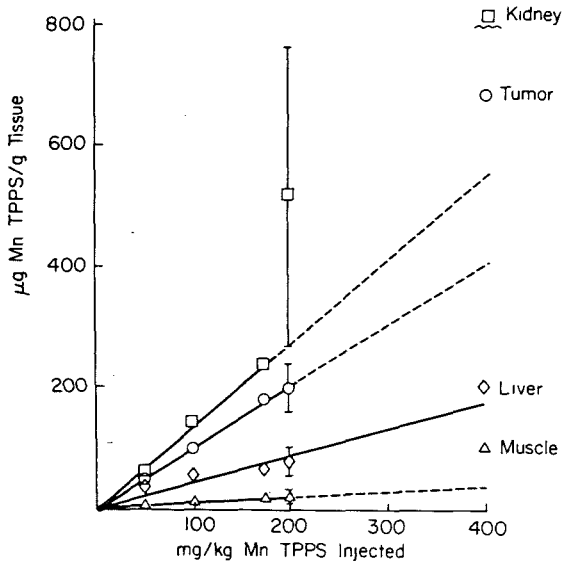

Fig. 6 Relation between dose of "Mn (III)$TPPS_4$" (see text) and concentration in mouse tissues. From R.J. Fiel et al: "Proton relaxation enhancement by manganese (III)$TPPS_4$ in a model tumor system" (Ref 24). By permission of the Pergamon Press plc, Elmsford, NY.

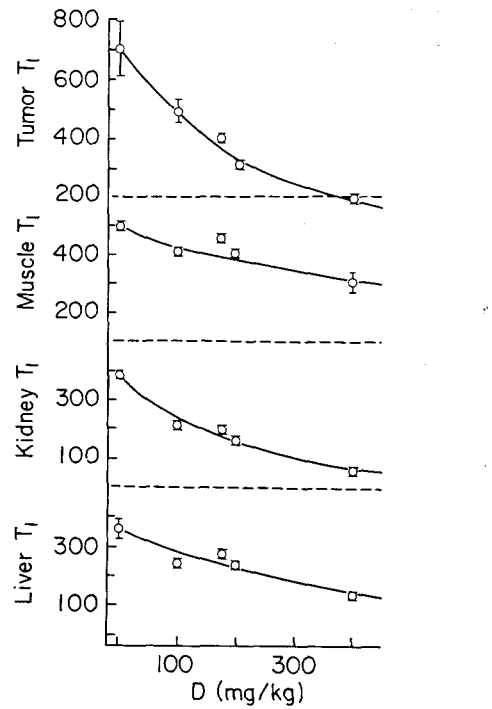

Fig. 7 Relation between dose of "Mn (III)$TPPS_4$" (see text) and T1 relaxation times of mouse tissues. Same source as Fig. 6.

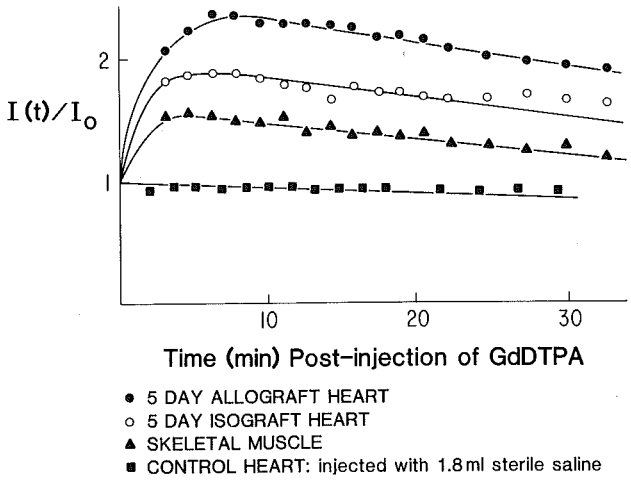

Fig. 8 Effect of Gd DPTA (see Table 1) on signal intensity in rat tissues. Io=pre-injection intensity. I(t)=post-injection intensity at time (t).

easily than non-rejecting hearts was pre-injection T2. Significant changes in relaxation times have been found in rejecting human cardiac transplants (26) but the clinical relevance of our Gd DPTA findings in rejection must still be tested.

In summary, dose-response relationships exist for diagnostic drugs as they do for therapeutic drugs but several classes of diagnostic drugs show special aspects of these relationships.

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Discussion - Dose-response relationships of diagnostic drugs

R.J. Temple

I have the feeling that most drugs used as diagnostic aids are not subjected to a systematic study such as those that you have described. I presume that this is due in part to the difficulty in finding a "gold standard" for the outcome, making it hard to measure sensitivity and specificity. Are you aware of any systematic attempts to study drugs such as saralasin, that are used as diagnostic agents?

E.A. Carr

I know of very few. You touched on two important points. First of all, you have to have a gold standard in order to study a variety of doses. If you are testing a new test, how are you going to know the diagnosis is right anyway? Your gold standard may be prolonged clinical observation or it may be something invasive such as a biopsy. Both of these discourage expanding the study by using a number of doses. The second point concerns a common strategy for something like saralasin. Instead of exploring different doses, one takes a single dose that will have an effect on just about everybody; one then looks for a demarcation point, and decides that anybody whose blood pressure has dropped more than this is in the abnormal group, and anybody who does not is in the normal group. Physicians tend to be conservative with doses of diagnostic drugs since, even in the best practice of medicine, some patients who get a diagnostic drug will prove to have no disease at all. Therefore toxic effects are particularly unacceptalbe.

J. Bigorra

In some European countries, allergens are widely used to treat atopic patients. Could you comment on that?

E.A. Carr

You mean for example, to try to develop blocking antibodies in patients with hay fever? Here again physicians start with very small doses and do notice differences in response. Elmer Becker, years ago, studied that type of hyposensitization and looked at a

different kind of dose-response curve, namely what fraction of patients will respond at all as you raise the dose. He could clearly show that some patients were exquisitely sensitive and would respond to a very small dose while others would take a bigger dose before they had any reaction. Nevertheless, he was still measuring all-or-none response. But if you ask your allergist friends, who have seen more allergic patients than I have, I suspect they may have seen graded reactions as they hyposensitize.

D.S. Davies

I just want to mention that it is quite common to do dose-response studies in skin tests with different antigens and in the evaluation of antiasthmatic drugs. One does get a nice graded response in atopic individuals.

E.A. Carr

I should add one last point. Although there have been reviews of thousands of skin tests to penicillin, for example, and it is generally a remarkably safe procedure, there is still one convincing report from the 1970's about a patient who died promptly in anaphylaxis after a scratch test with 300 nanograms. Everything was done the correct way, but the patient died!