

DETERMINANTS OF PHARMACOLOGIC EFFECT

Drug therapy is the major intervention available for the amelioration and palliative care of disease. The predominant role of pharmacotherapy in the management and prevention of disease necessitates a clear understanding of factors that influence the response to xenobiotics.

1

***Xenobiotic* is a term used to refer to any compound to which the body is exposed but which is foreign to the body. This could be a drug or environmental chemical.**

Importantly, those principles that govern the disposition of and response to chemicals are the same with which we are concerned as it relates to drugs.

2

PRIMARY MEANS TO QUANTIFY DRUG EFFECT

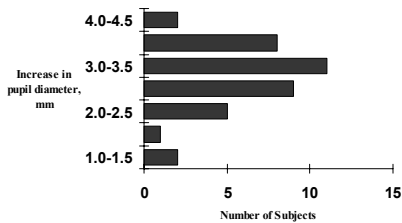
- ONSET**
- DURATION**
- INTENSITY**

3

**Evaluation of the onset,
duration and intensity of
xenobiotics leads to the
observation of an important
reality about
pharmacologic effect:
VARIABILITY**

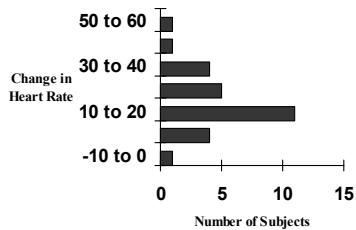
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The figure below illustrates the variability in response to one drop of phenylephrine 30 mg/ml instilled into the conjunctival sac of 39 subjects. Data from Bertler and Smith, *Clin Sci* 40:403. 1971.

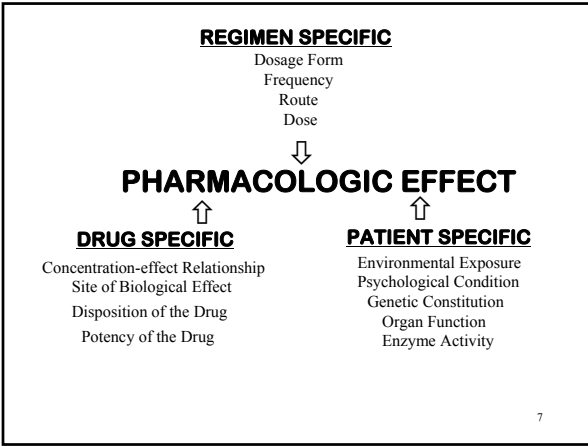


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The figure above illustrates the variability in response to intramuscular atropine 0.02 mg/kg in a group of 27 subjects. Data from Smith and Rawlins, *Variability in Human Drug Response*, 1973, p. 1-2.

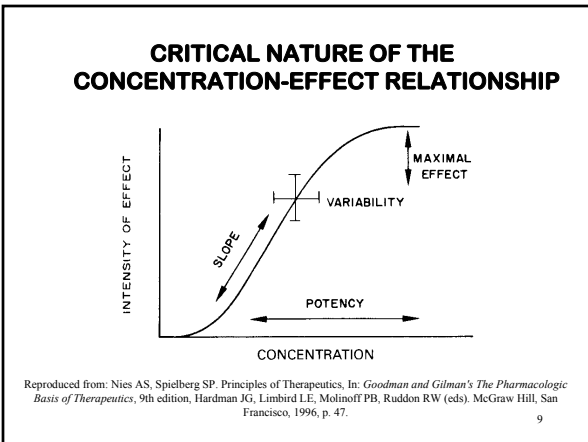


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**DRUGS
 VS
 DRUG PRODUCTS**

8



Relationship between seizure control and plasma phenytoin concentration.

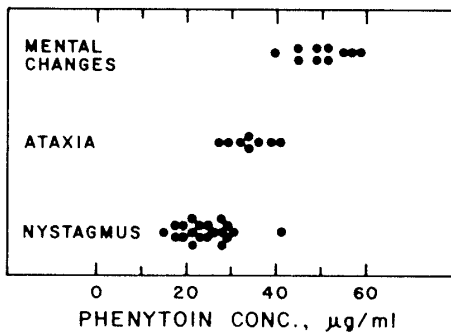
Phenytoin Conc (mg/L)	# Patients	# Pts without seizures during 2 months	% Seizure Free
0 to 9.9	95	41	43
10 to 19.9	33	24	72
>20	20	19	95

(Data from Lund L. *Biological Effects of Drug in Relation to Their Plasma Concentration*. Davies DS, Pritchard BNC (Eds), MacMillan Press, 1973, p. 227.)

Relationship Between Phenytoin Serum Concentration and Gingival Hyperplasia

Grade of Hyperplasia	# of Pts	Phenytoin Conc (mg/L)
0	75	3.0
I	26	3.8
II	99	9.5
III	27	18.4

(Data from: Kapur et al. *Dev Med Child Neurol* 15:483, 1973.)



Reproduced from: Gibaldi M. *Biopharmaceutics and Clinical Pharmacokinetics*, 4th edition, 1991, p. 356

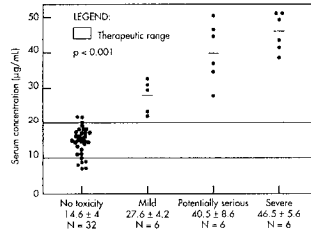
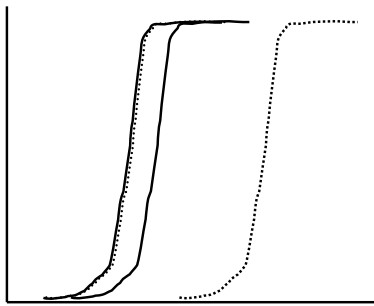


Figure 17.2. Correlation between the frequency and severity of adverse effects and plasma concentration of theophylline (mean ± SD) in 50 adult patients. Mild symptoms of toxicity included nausea, vomiting, headache, and insomnia; a potentially serious effect was sinus tachycardia, and severe toxicity was defined as the occurrence of life-threatening cardiac arrhythmias and seizures. Adapted from Hendoles and Weinberger, 1980, with permission.

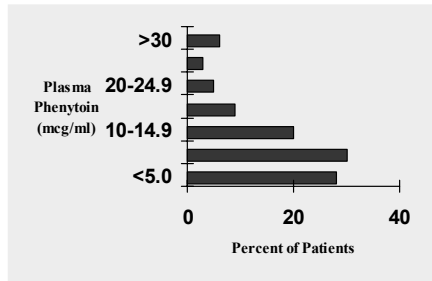
Reproduced from: Shargel L, Yu ABC. *Applied Biopharmaceutics & Pharmacokinetics*, 4th edition, 1999, p. 510.

Effect



Log Concentration

Frequency of plasma phenytoin concentrations in a group of ambulatory patients, all of whom were receiving 300 mg per day.



(Data from: Koch-Weser J. *Eur J Clin Pharmacol* 9:1-8, 1975)

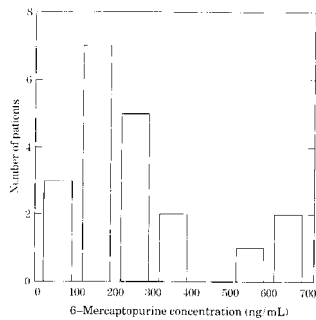


Fig 3. Distribution of peak 6-mercaptopurine concentrations achieved in a group of 20 patients receiving an oral dose of 1 mg/m² (courtesy, data, Sulh et al¹).

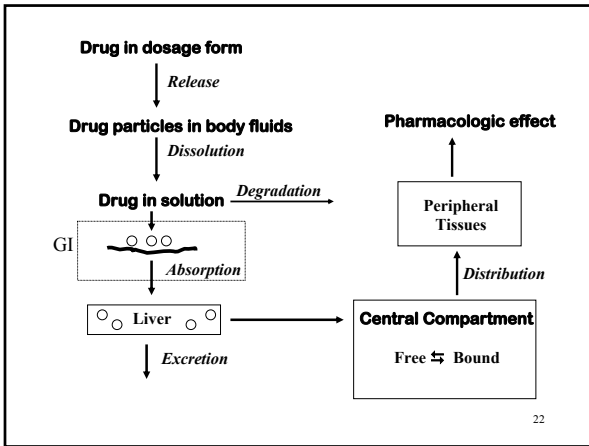
Reproduced from: Galinsky RE, Svensson CK. Basic Pharmacokinetics, In: Gennaro AR (ed), Remington: The Science and Practice of Pharmacy, 20th edition, 2000, p. 1128

The foregoing can be summarized to note important facts related to drug effect:

- **There is significant variability in drug response**
- **Pharmacologic response is dependent, in large measure, on the concentration of drug achieved at the site of action**
- **There is significant variability in the drug concentration achieved after a standard dose of a drug**

What conclusion do we draw from these facts?

Variability in drug concentration makes a major contribution to the observed variability in pharmacologic effect.



Pharmacokinetics
 The study of the absorption, distribution, biotransformation and elimination of xenobiotics.

Pharmacodynamics
 The study of the biochemical and physiological effects of xenobiotics and their mechanisms of actions

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