13 - 2. Indices of safety and efficacy

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© SPMM Course 2. Indices of safety and efficacy: Quantal or dose-response curves: Quantal curves plot the percentage of a population showing a specified, predefined categorical drug effect against the dose or log dose administered. The doseresponse curve plots the drug concentration against the continuous effects of the drug. Using these curves, the median effective dose, or median toxic doses can be determined. The median toxic dose is the dose at which 50% of patients experience a specific toxic effect, and the median effective dose is the dose at which 50% of patients have a specified therapeutic effect. In addition, using these curves the range of intersubject variability in drug response could be studied. Steep D-R curves reflect little variability; flat D-R curves indicate great variability in patient sensitivity to the effects of a drug. The therapeutic index can be determined using these curves. Therapeutic index: It is the relative measure of the toxicity or safety of a drug. It is defined as the ratio of the median toxic dose to median effective dose. In other words, it is the ratio of the minimum plasma concentration causing toxic effects to that causing a therapeutic effect. This can vary according to the toxic symptom specified for a given drug. For example, the gastrointestinal toxicity of lithium can occur at a lower plasma concentration than that for seizures. In the laboratory this is usually determined using the median lethal (LD50) and median toxic dose (TD50) in animal studies. In humans, this is identified using ‘minimal’ effective and ‘minimal’ toxic doses using trial data. Note that the term therapeutic index is only relevant when considering dose-dependent side effects; it is not useful when studying idiosyncratic reactions. Therapeutic index range: Certain drugs such as lithium, carbamazepine and phenytoin have a narrow range of plasma levels within which the efficacy is optimum and toxicity is less evident; crossing this range on higher side will increase toxicity while on the lower range will reduce efficacy. Drugs with the low therapeutic index or narrow therapeutic range will require plasma monitoring. Therapeutic window: This term is often confused with therapeutic safety range. In fact, this term is used to describe a specified plasma concentration value, only within which certain drugs appear to have a therapeutic efficacy. This does not concern the side effects or toxicity. Imipramine, nortriptyline, and desipramine have a curvilinear relationship when plasma levels are plotted against the therapeutic response, i.e. very high or very low levels do not help the patient.

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