Review Med Toxicol Adverse Drug Exp. 1988 Mar-Apr;3(2):128-65.

Pharmaceutical excipients. Adverse effects associated with inactive ingredients in drug products (Part I)

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PMID: 3287089

Abstract

Excipient reactions have resulted from the use of clearly toxic substances (e.g. diethyleneglycol), the use of certain excipients in a susceptible group (e.g. very low birthweight neonates, patients with large surface area burns, patients with a history of asthma or contact dermatitis), the alteration of an excipient mixture resulting in altered bioavailability (e.g. phenytoin), and the deliberate or inadvertent extradural administration of preserved medications intended for intravenous use. Inadvertent excipient overdose has also occurred when unusually large doses of a drug containing a preservative were used [chlorbutol in morphine, ethanol in glyceryl trinitrate (nitroglycerin)]. Most excipient problems are preventable with knowledge of the currently available formulation. Government drug regulatory agencies have largely prevented introduction of a new toxic excipient; however, the new use of previously approved (but not adequately studied) excipients continues to result in unfortunate tragedies (e.g. the E-ferol incident). Populations at risk should be monitored carefully. Very low birthweight infants (less than 100g) have a well-demonstrated intolerance to many excipients, particularly during the first 2 weeks of life. Research should be directed toward development of non-preserved medications and safer diluents for this population. Drugs and excipients which have previously been demonstrated to be safer in other populations (e.g. doxapram) should be meticulously studied in this age group before widespread use is recommended. Asthmatic patients comprise another population that are frequently sensitive to excipient toxicity. In some cases, as in sulphiting agents, which are ubiquitous in foods as well as in medications, total avoidance may not be possible and prophylactic therapy may be beneficial. Inactive ingredients are clearly not consistently inert in their biological activity and therefore should not be listed as such. A more useful and concise term is excipient. It is highly recommended that all pharmaceutical manufacturers list all their excipients and make this available to practitioners and drug information centres. Alternatively or additionally, the package insert should list these excipients in accordance with good manufacturing procedures. This disclosure will help to determine the relative frequency and magnitude of problems (bioequivalence, toxicity, etc.) that excipients may have in the population, as well as enabling susceptible patients to avoid inadvertent exposure.

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