d. Paradoxes with drugs for treating bronchial constriction

Isoproterenol, a drug used for treating asthma, can cause symptoms of asthma, when administered in excessive doses. In an article on various issues relating to package inserts, Goyan (148) wrote, "the first patient package insert was required by FDA in 1968, when it was recognized, at least implicitly, that some drugs could not be used properly unless certain information was conveyed to patients as well as to prescribers or dispensers. Thus, in June 1968, FDA required that each isoproterenol inhalation drug dispensed to a patient bear a two-sentence warning on the container advising of an association between repeated and excessive use and severe paradoxical bronchoconstriction. FDA required the warning because inappropriate use by patients was actually causing the condition the drug was intended to treat." This particular adverse drug reaction may have been due, in part, to the fact that the drug contains sulfite. Sulfite has the well-known effect, at least in asthmatics, of causing allergic-type symptoms, including anaphylaxis (149). The package insert for isoproterenol, "sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people" (150). Moreover, the package insert explicitly warns of an additional paradox with this drug, "isoproterenol hydrochloride injection has paradoxically been reported to worsen heart block" (151). Still another drug for treating bronchial constriction or spasms, albuterol, has also been documented to have the paradoxical adverse drug reaction of causing bronchial spasms (152). Yet another bronchodilator, ipratropium, has also been found to have the "paradoxical" effect of causing bronchial spasms. According to the package insert, "[i]nhaled medicines, including ATROVENT HFA Inhalation Aerosol, may cause paradoxical bronchospasm" (153).

IV. MONITORING AND EVALUATING ADVERSE EVENTS

In clinical trials, AEs need to be monitored and captured, transmitted to various personnel stored in a database, and evaluated. Some AE data are captured on a scheduled and orderly basis, such as data from the laboratory analysis of blood and urine. But other AEs, such as vomiting, seizures, or death, need to be captured as soon as they occur. For any given clinical trial, at least in the context of oncology, about 50 AEs occur per study subject, with about 2,000 to 3,000 AEs in all during the lifetime of the clinical trial (154).

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