Adverse Drug Events Related to Dosage Forms and Delivery Systems

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Summary

While some of the adverse events caused by the administration of medicines are specifically attributable to the drug molecule, a proportion arises because of the chemical, biological and physical nature of the formulation. The effects may be compounded by certain patient factors, an incomplete understanding of the behaviour of the formulation or the coadministration of other drugs. This review examines adverse drug reactions and other adverse events arising from the nature of the dosage form or formulation used. These adverse effects may be the result of local irritation/toxicity, hypersensitivity or allergic reactions, systemic effects...
from essentially local therapies, or idiosyncratic reactions in a small number of individuals. In certain cases where the exact nature of the formulation is unknown, adverse events cannot be attributed to any single ingredient. In addition, the total of all ingredients of a formulation, even where details of the formulation are clear, may give rise to abnormal behaviour of the formulation in vivo. Often the desired objective of a particular specialised formulation leads to an unforeseen but related adverse effect, and in certain instances these events are completely unpredictable and at variance with the perceived objectives of the formulation.

The formulation of drugs into medicines allows for accurate dosage, convenience and ease of administration, assured stability and, in certain situations, controlled delivery or drug targeting to specific tissues or organs. The changes associated with the formulation process can range from the apparently straightforward, such as the conversion of a drug into a solution for injection, to the production of more complex formulations which require the incorporation of drugs into liposomes, nanospheres or microspheres. Some formulations are deceptively simple and may contain apparently innocuous materials which prove in some individuals to be biologically active. It may also be that the nature of the dosage form, such as a sustained release tablet, causes it to behave abnormally in a small group of patients. The adverse reactions sometimes encountered with medicines may be attributable not to the drug but to an excipient, or even to the nature of the dosage form being used. However, it is more likely that it is the way in which the drug is delivered, or that some synergy between drug and excipient leads to the adverse effect.\[1\] There are other modes of involvement of the formulation when, designed for local effect, they give rise to unwanted systemic effects or local irritation. Figure 1 details schematically the probable sources of adverse drug reactions, including those that pertain to the nature of the dosage form.

Adverse drug reactions involving formulations are in general the result of:

- direct tissue toxicity, such as the gut mucosal damage associated with slow release potassium chloride tablets\[2\]
- augmented effects of the drug, either dose-related or compounded by an underlying pathological state
- a synergistic interaction between 2 agents, e.g. the possible exacerbation of the ulcerogenic action of indomethacin ('Osmosin') by coformulation with potassium chloride\[3\]
- the manifestation of an allergic or immunological effect, e.g. allergic reactions to the solubiliser 'Cremophor EL' in 'Taxol'\[4\]
- an idiosyncratic response.

Idiosyncratic responses occur in a relatively small proportion of patients but, because they are largely unpredictable, place a great strain on hospital resources. In some cases there may be only suspicions as to the cause of the toxic effects, as in the recently suggested link between polymers used in the enteric coating of pancreatic enzyme–containing microspheres and the observed colonopathy.\[5\] In a few cases, the adverse effect may be caused by the known effect of some ingredients, such as the carcinogenic impact of carbohydrate sweeteners in paediatric liquid products.\[6\]

Adverse drug events related to the delivery system may originate from the drug itself but be exacerbated by the formulation, which might rarely include the chemical form. An example is the production of potentially neurotoxic concentrations of plasma bismuth (15 to 232 mg/L) after the oral administration of tripotassium dicitrato bismuthate (bismuth subcitrate) compared with the markedly reduced concentrations of plasma bismuth (0.7 to 2.6 mg/L) on administration of bismuth subcarbonate.\[7\] Where a drug elicits a homeostatic response (e.g. prazosin, nifedipine or furosemide (frusemide)) which ultimately contributes to the observed pharmacodynamic response, the administration of a