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Spontaneous Reports and Pharmacogenetics

The Role of the Pharmacovigilance Centre

A commentary, 'Pharmacogenetics and Pharmacovigilance',[1] was recently published concerning our study[2] in the same issue of the journal. The goal of our study was to gain insight into the feasibility of selecting and genotyping patients based on adverse drug reaction (ADR) reports received by the Netherlands Pharmacovigilance Centre. The main question posed was whether pharmacovigilance centers can provide the appropriate clinical and scientific information needed for the decision to genotype a patient who has experienced an ADR that is possibly due to a genetic polymorphism. Pharmacovigilance centres assess suspected ADRs reported by health professionals and patients. A lack of certainty about the causal relationship should not prevent health professionals and patients from reporting these ADRs; a report of a suspected ADR rarely implies a certain causal relationship between the suspected drug and the reported event. In clinical practice, the etiology of a clinical event is not always known, even after thorough examination and testing. ADRs are no exception. In addition, the event may have a multi-factorial etiology. One of these factors may be the existence of an aberrant pharmacokinetic mechanism that may explain an increased likelihood of a particular patient developing ADRs.

Assessors of ADR reports sometimes have access to specific information that should preferably also be shared with those who have actual contact with the patients. This usually applies not only to the number of reports in the (national) ADR database and information from the literature, but assessors may also know of evidence of a possible mechanism that may contribute to the occurrence of an ADR. Limiting the role of a pharmacovigilance centre to merely a reporting centre, and withholding this information from a treating physician, could be considered as unethical. A striking example of the duty to inform patients about a genetic variant that causes serious adverse effects is the case of pseudocholinesterase. In 1956, Lehman and Ryan[3] discovered a familial factor in the 'idiopathic' low pseudocholinesterase level associated with suxamethonium chloride toxicity. Today, no-one would overlook a serious ADR report involving suxamethonium chloride or mivacurium chloride without recommending pharmacogenetic testing. What about a report on azathioprine myelotoxicity[4] – should a pharmacovigilance centre suggest a thiopurine methyltransferase (TPMT) test? Would just registration – without reporting back our knowledge – be ethical? In our view, pharmacovigilance centres do indeed have an 'advisory and educational role'.

Spontaneous reporting systems primarily have a signalling function. The causal relationship between the reported ADR and the suspected drug is rarely certain. Nevertheless, it is the task of a pharmacovigilance centre to reduce this uncertainty as much as possible. One way of doing this is by asking for additional information from the reporter about the circumstances around the ADR or any additional testing that has been carried out. For all parties involved, it is important to investigate all factors that may have contributed to the occurrence of the ADR. Also, the existence of a pharmacogenetic cause should be considered. Once a polymorphism has been established, the patient should be informed.

Providing information to healthcare professionals should be distinguished from recommending genotyping. The feedback we give to healthcare professionals merely suggests that factors such as pharmacogenetic involvement might have a role to play. Having knowledge of a possible mechanism does not imply that pharmacogenetic tests have to be carried out. Clinical judgement plays a key role in this process. Taking into consideration all other possible reasons for the ADR, it is up to the physician to decide whether or not to have the patient genotyped. In addition, knowledge of an enzyme deficiency can help the physician to choose a better medication (in the correct dosage) for the patient next time.

Another point of criticism raised in the commentary[1] referred to the exclusion of patients with allergic reactions. In patients with allergic reactions, kinetic factors very rarely play a role. As in other type B reactions, dose dependency is not likely. For this reason we decided not to include reports with these types of ADRs.

We are only just beginning to understand the role of pharmacogenetics in the pathogenesis of ADRs. Our study was a pilot study to get experience with reporting back any potential pharmacogenetic involvement in the pathogenesis of ADRs. The study has the usual limitations of a practical and naturalistic study on reported ADRs: the impossibility of obtaining blood from deceased patients retrospectively; limitation to the most prevalent pharmacogenetic factors – cytochrome P450 (CYP) 2D6, CYP2C19 and CYP2C9; the voluntary nature of patient participation; and the difficult classification and broad spectrum of the reported ADRs. As with any new methodology, its actual value only becomes evident after gaining enough experience with it. Creating awareness and informing healthcare professionals and patients about the possibility of pharmacogenetics as a causal factor is the first step in this process. This is exactly what our study aimed to convey.

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