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Use of the Dose, Time, Susceptibility (DoTS) Classification Scheme for Adverse Drug Reactions in Pharmacovigilance Planning

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Abstract

In the process of conceiving a pharmacovigilance plan, as proposed in the International Conference on Harmonisation E2E guideline, the challenge will be how to address possible safety issues with a set of appropriate pharmacovigilance methods. For successful planning, the various and sometimes complex dimensions of the adverse drug reaction in question have to be appropriately described. In order to accommodate these better, a 3-dimensional approach, based on dose, time and patient susceptibility, has recently been proposed (the DoTS model). This approach offers a way of presenting the various dimensions of the problem graphically. The aim of this article is to propose how an extended DoTS model, applied to three different scenarios, could give a better understanding of adverse drug reactions and assist in preparing a pharmacovigilance plan.

The limitations of the current system for safety surveillance of drugs have been recognised in recent years by regulators and the pharmaceutical industry. One manifestation of the efforts to deal with these limitations is the International Conference on Harmonisation (ICH) E2E Guideline on Pharmacovigilance Planning.[1] Central themes in the guideline are the need for a more proactive approach and the integration of premarketing development and postmarketing surveillance. The guideline recommends the preparation of a safety specification and a pharmacovigilance plan that might be submitted at the time of application for a marketing authorisation. The safety specification should be a summary of the important identified risks of a drug, important potential risks and important missing information. By outlining a strategy involving a set of pharmacovigilance methods, the pharmacovigilance plan will then specify how the concerns raised in the safety specification will be addressed.

For pharmacovigilance planning to be successful, the various facets of an adverse drug reaction need to be characterised. With the frames of reference currently in use, adverse drug reactions have generally been classified into type A reactions (predictable and dose dependent) or type B reactions (unpre-

dictable and dose independent). Although convenient, this classification has been suggested to be too simplistic, and despite its later extension,[2] it is still inadequate to the task of classifying all adverse drug reactions. In order to accommodate better the multiple dimensions of adverse drug reactions, a 3-dimensional approach, based on dose, time and patient susceptibility, has recently been proposed (the DoTS model).[3] The proposal is expected to provide important insights for drug development and regulation, pharmacovigilance, monitoring patients, and the prevention, diagnosis and treatment of adverse drug reactions.

The aim of this article is to propose how an extended DoTS model, applied to three different scenarios, could give a better understanding of adverse drug reactions and assist in the preparation of a pharmacovigilance plan.

1. The Dose, Time, Susceptibility (DoTS) Approach and Some Extensions

The DoTS approach assumes that all adverse drug reactions, including immunological reactions, are dose dependent and that they should be classified according to the relation between the dose-response curve for benefit and the dose-response curve for harm. Reactions are divided into those that occur at supratherapeutic doses (toxic effects), at standard therapeutic doses (collateral effects) and at subtherapeutic doses in susceptible patients (hypersusceptibility reactions).[3] There are two patterns of time course of an adverse drug reaction: time-dependent and time-independent reactions. The latter can occur at any time during treatment. Time-dependent reactions can be further categorised into six subtypes: rapid, first dose, early, intermediate, late and delayed. The third dimension in the DoTS model is related to patient susceptibility factors, e.g. genetic variation, age, sex, physiological variation, exogenous factors and diseases. As a further elaboration of the DoTS model, the probability of an adverse drug reaction can be described in the form of sets of 3-dimensional graphs (figure 1).

Some modifications of this approach could enhance its suitability for pharmacovigilance planning. When conceiving a strategy for safety surveillance of a new drug, in addition to the variables in the original model, consideration of the baseline incidence rate of an event and the sizes of relevant subgroups are of interest.[1,4] The former variable has implications for the choice of pharmacovigilance method, whereas the latter is of importance to the public health perspective. Hence, in the three scenarios presented in this article, an attempt to

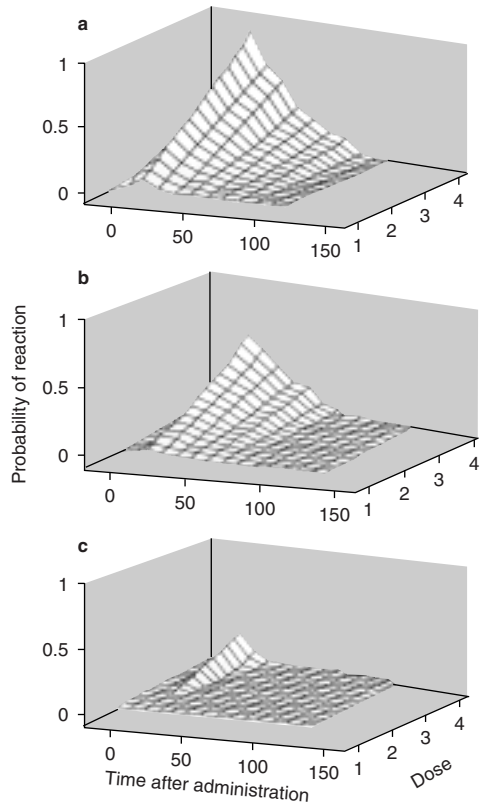

Fig. 1. Graphs showing how probability of adverse drug reaction (y-axis) might vary with variations in time after administration (x-axis, arbitrary units) and dose (z-axis, arbitrary units) in people with (**a**) high, (**b**) medium and (**c**) low susceptibility for having an adverse effect of intermediate type. Reproduced from Aronson and Ferner,[3] with permission from the BMJ Publishing Group.

integrate all the relevant information is presented in the respective graphs. Also, the segments of the surfaces investigated by a particular pharmacovigilance method are indicated in the figures for the target populations. The risk of harm is expressed as the incidence rate, and since the baseline incidence rates are clearly indicated it is possible to discern absolute and relative risks. Stratification by co-variates (i.e. sources of susceptibility) considered to be most relevant appears below the graphs of the overall target patient population. Obviously, more than one co-variate can be used for stratification; however, this will increase the complexity of the exercise.

2. Pharmacovigilance Methods

The International Conference on Harmonisation (ICH) E2E guideline lists six groups of pharmacovigilance methods that could be represented in a pharmacovigilance plan.[1] A summary of these methods, complemented with some brief comments on their qualities, appears in table I. The best method to address a specific drug-related safety concern can vary, depending on factors such as indication, patient population or dose regimen (e.g. intermittent or continuous). Also, characteristics of the adverse reaction, such as baseline incidence, severity, and dose dependence or induction time, have implications for the preferred study design. The method chosen can also depend on whether an identified risk, potential risk or missing information is the issue and whether signal detection, evaluation or safety demonstration is the main objective of further study. The details of the appropriateness and constraints of various methods in addressing specific issues are beyond the scope of this article.

3. Three Scenarios

Drugs A, B and C in the following scenarios are fictitious; however, the types of emerging safety profiles that they exemplify are commonly seen and have been inspired by the properties of some drugs in development or on the market. In the scenarios, the drugs are assumed to be in early clinical development (phase I–II) and are intended to be used for continuous long-term treatment. For ethical reasons, most information on supratherapeutic doses, whether administration is short- or long-term, would have to rely on spontaneous reports in all three scenarios. Obviously, the same applies to adverse effects during pregnancy. At this stage, there is some information from dose-ranging, short-time studies – this is marked with a light grey surface in all three scenarios. All other surfaces are based on various assumptions and appear as a mesh. The areas planned to be investigated in the phase III programme are contained within bold lines. It should be noted that the scales for treatment duration (x-axis) are adapted to the properties of the drug and the patient population, and thus vary across the graphs for Drugs A, B and C. Arbitrary units are used to indicate the incidence rates (y-axis). These units are comparable within a scenario but not across the three scenarios. Doses (z-axis) are categorised into subtherapeutic, therapeutic and supratherapeutic. Finally, in all three scenarios, safety surveillance should include drug utilisation studies in order to assess whether the 'real life' patient population agrees with the intended target population with respect to co-variates of relevance (e.g. age, sex or concomitant medications).

3.1 Drug A

Drug A is an inhaled glucocorticoid under development for the treatment of asthma. It is expected that its properties could lead to most effects being exerted locally and that the systemic effect would be limited.[5] Hence, compared with currently marketed inhaled glucocorticoids, there would be a lower incidence of osteoporotic fractures when used in elderly patients (figure 2). At this stage, the target population is stratified into patients aged <50 years (figure 2b) and those aged >50 years (figure 2c). The assumed proportions appear in the top grey bar. If a

Table I. Pharmacovigilance methods proposed by the International Conference on Harmonisation E2E Guideline on Pharmacovigilance Planning[1]

Group of methods	Method	Comments
Passive surveillance	Spontaneous reports	Primarily used to generate signals on rare adverse events not detected in the premarketing studies. Spontaneous reports can also provide important information on at-risk groups and risk factors. The method is associated with a high occurrence of false positive signals
	Case series	A case series of reports can occasionally be used to establish causal relationships between a drug and an event
Stimulated reporting		Various methods used to encourage reporting by health professionals. The information is subject to the same limitations as passive surveillance
Active surveillance	Sentinel sites	The method aims to ensure complete and accurate data on reported adverse events from a sample of sites. Most efficient for drugs used primarily in institutional settings
	Drug event monitoring	Patients are identified from prescription data. Follow-up questionnaires are then sent to each prescribing physician or patient at prespecified intervals to obtain outcome information
	Registries	A registry is a list of patients with the same characteristic(s) with respect to disease or specific exposure. Information can be collected using standardised questionnaires in a prospective fashion
Comparative observational studies	Cross-sectional study (survey)	Data are collected on a population of patients at a single point in time, regardless of exposure or disease status. These types of studies are primarily used to gather data for surveys or for ecological analyses
	Case-control study	The exposure status of cases and controls is compared using the odds ratio. These studies are particularly useful when the goal is to investigate whether there is an association between a drug(s) and one specific rare adverse event, as well as to identify risk factors
	Cohort study	A population at risk for the disease (event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. The method is useful when there is a need to know the incidence rates of adverse events
Targeted clinical investigations	Pharmacodynamic/kinetic studies Genetic testing Studies of drug-drug interactions	When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction
Descriptive studies	Natural history of disease	Studies that examine specific aspects of adverse events, such as the background incidence rate of, or risk factors for, the adverse event of interest, can be used to assist in putting spontaneous reports into perspective
	Drug utilisation study	These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, sex, concomitant medication and other characteristics. Drug utilisation studies can be used to examine the relationships between recommended and actual clinical practice

decision were made to include patients with chronic obstructive pulmonary disease in the target population, the DoTS graphs would have to be modified accordingly. In particular, the proportion of patients aged >50 years would increase, as would the baseline incidences.[6] Based on the DoTS terminology, osteoporotic fractures caused by drug A could be classified as being a collateral effect, occurring at a late stage with age as one source of susceptibility.

Given that systemic effects of inhaled glucocorticoids depend on dose and treatment duration,[7] it is reasonable to assume that very little information about osteoporotic fractures will emerge from the phase III programme (area within the bold line). However, in trials with limited treatment durations,

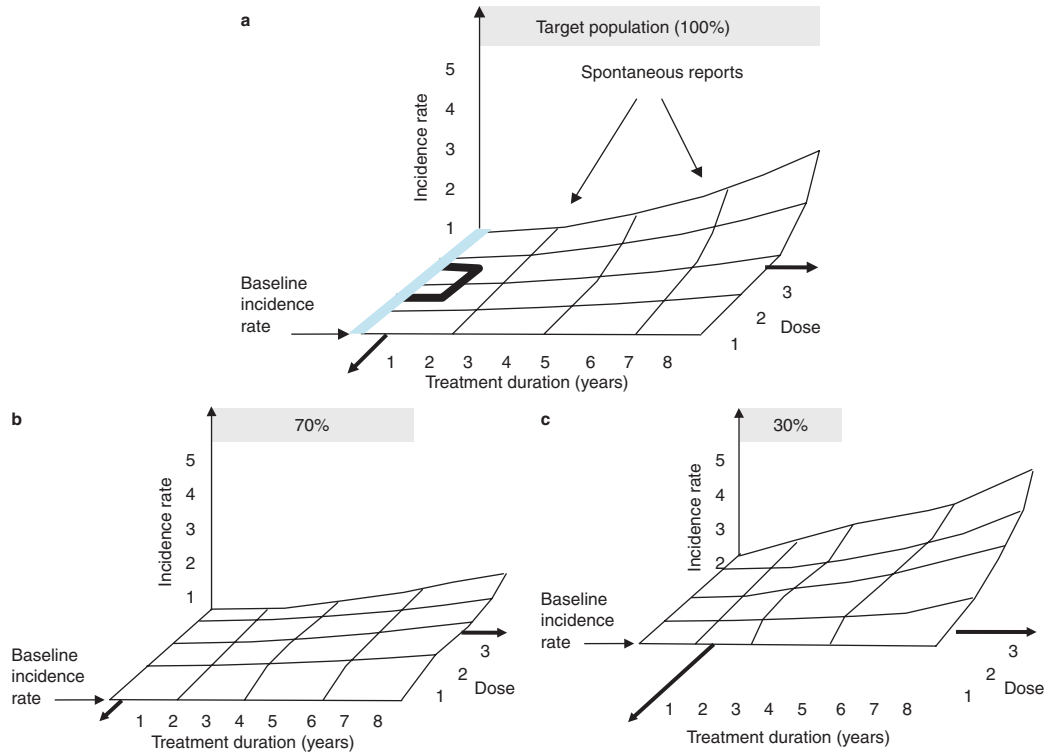

Fig. 2. Dose, time, susceptability (DoTS) graphs for drug A, an inhaled glucocorticoid intended for the treatment of asthma. The assumed incidence rates of osteoporotic fractures (arbitrary units), in relation to dose and treatment duration, are shown for (**a**) the overall target population, (**b**) the proportions of patients aged <50 years and (**c**) aged >50 years. The baseline incidence rates of osteoporotic fractures differ between the two subgroups defined by age (**b** and **c**). Doses are (1) subtherapeutic, (2) therapeutic and (3) supratherapeutic, and treatment duration is up to 8 years. The light blue surface is studied by means of dose-ranging, short-time trials, and areas planned to be investigated in the phase III programme are contained within bold lines (up to 1 year). Spontaneous reports, represented by the black arrows, are used to obtain information on the effects of short- and long-term administration of supratherapeutic doses.

measurements of surrogate endpoints for systemic effects (e.g. hypothalamic pituitary adrenal axis suppression) could generate relevant information.[8] When assessing the outcome in the longer perspective, given that the reaction has a high baseline incidence and a long induction time, spontaneous reports will be of little value when quantifying the risk. A case-control study may be an alternative and, as market launch approaches, planning could involve finding a setting in which the information of relevance to the reaction could be retrieved. Since the outcome is fairly common and would normally involve hospitalisation, studies in hospital medical records would be useful for case identification. With respect to the use of drug A, cumulative rather than current exposure would be of interest. Hence, drug utilisation estimates based on interviews would be unreliable because of recall bias, and prescription registries would be the preferred data source. A major challenge in this scenario is that the drug could be marketed as the preferred treatment for vulnerable subjects (e.g. elderly patients). In that case, confounding by indication would probably have a negative impact on the validity of observational studies. In order to reduce this kind of bias, the use of propensity scores or ecological analyses has been proposed.[9] Also, long-term, randomised, controlled trials could theoretically be used in order

to assess safety. However, problems associated with costs and logistics, and the fact that these studies tend to adopt observational characteristics over time,[10] limit this option.

The first set of DoTS graphs, as exemplified in figure 2, could form the basis for discussions regarding how dose and treatment duration are related to the risk of osteoporotic fractures. Would it be reasonable to assume that these associations are continuous and linear? Or could there be critical thresholds after which the risk increased dramatically? What assumptions are made with regard to the relation between the surfaces of drug A and those of other marketed inhaled glucocorticoids? The issues raised would obviously prompt investigators to consider alternatives for an appropriate pharmacovigilance plan.

3.2 Drug B

Drug B is an immunosuppressive agent intended for the treatment of rheumatoid arthritis. In the early phase I–II programme, there were elevated liver function tests in some subjects. The pattern of increased levels of aminotransferases, alkaline phosphatase and bilirubin suggested a potential for hepatotoxicity.[11,12] Although factors related to the metabolism of the drug or the immune system are often implicated in hepatotoxicity, the details of the pathophysiology usually remain obscure. Drug B is considered to address an unmet medical need in a group of patients with a debilitating disease. Hence, some degree of risk and intensive monitoring schemes would probably be acceptable. In figure 3, a possible scenario is presented in which the reaction is assumed to occur after a few weeks of treatment. Based on the DoTS terminology, the hepatic injury caused by drug B could be classified as a hypersusceptibility reaction, occurring at an intermediate stage with some genetic variant as a source of susceptibility.

If the hepatotoxic reaction is rare, it is quite likely that clinical trials in phase III (the area within bold lines) will not include any susceptible patients, and this phase of the development programme may not yield much relevant information. Rather than spreading out assessment of liver function tests over the entire duration of the trials, an efficient study design should focus these investigations in the first month. Precise estimates of any induction time would be critical in order to decide whether the risk could be managed by withholding treatment in susceptible subjects before the drug caused irreversible liver injury. In the early postmarketing phase, based on the nature of the reaction (i.e. serious with a relatively short induction time and a low baseline incidence), a fairly high reporting rate could be expected, and spontaneous reports should be useful in identifying a safety signal. Also, complemented with drug utilisation data, a crude incidence rate can be estimated. In order to validate hepatotoxic reactions and identify possible risk factors, efforts to obtain follow-up information would be crucial. In particular, detailed information on concomitant drug use would be important in patients with suspected hepatotoxicity. Also, if possible, follow-up should include attempts to obtain blood samples for measurements of drug concentrations and genetic analyses. Although the science of pharmacogenetics is in its early stage, this evolving field may lead to the identification of genetic markers of susceptibility.[13] Further, active surveillance could be performed by initiating a registry of patients exposed to the drug, or by liaising with centres recording outcomes of interest (e.g. liver transplantation registries). If a case-control study is believed to be of interest, information on current exposure, rather than past or cumulative, would be of relevance. Thus, interviews would be an acceptable method of assessing exposure. Since factors associated with this type of toxicity are often genetic and concealed to the prescriber,

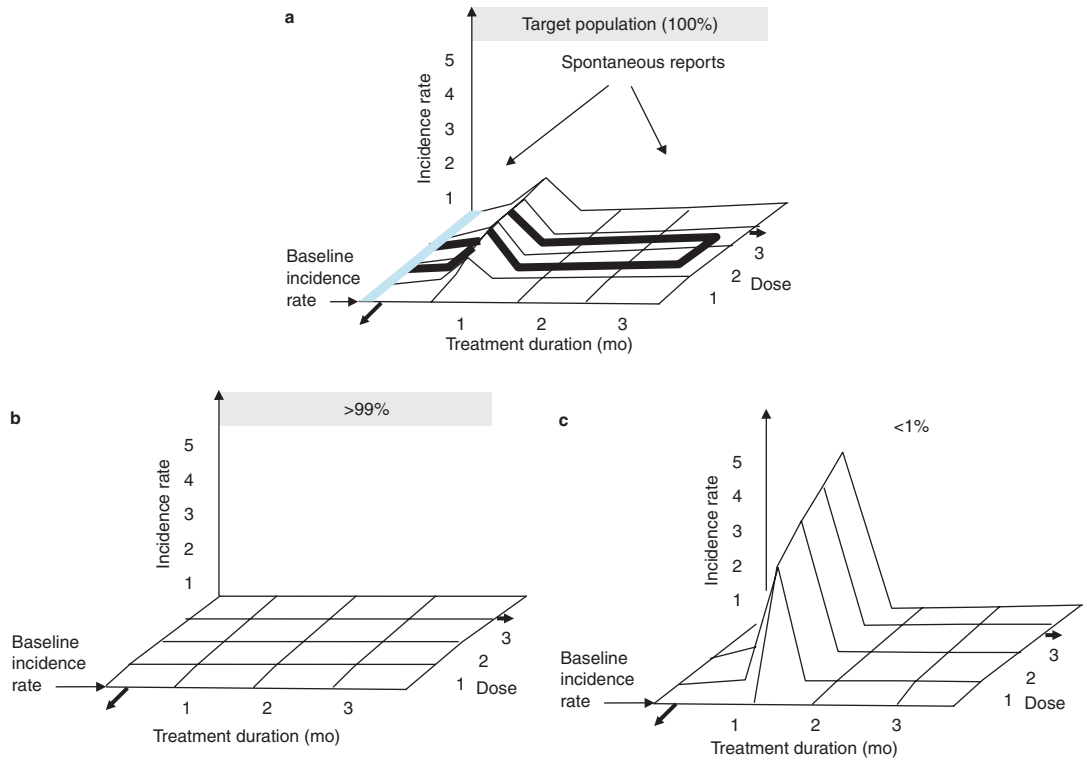

Fig. 3. Dose, time, susceptability (DoTS) graphs for drug B, an immunosuppressive agent intended for the treatment of rheumatoid arthritis. The assumed incidence rate of hepatotoxic reactions (arbitrary units), in relation to dose and treatment duration, is shown for (**a**) the overall target population, (**b**) the proportions of patients without a genetic susceptibility factor and (**c**) patients with a genetic susceptibility factor. In the absence of exposure to drug B, the baseline incidence rates of hepatotoxic reactions do not differ between the two subgroups (**b** and **c**). Doses are (1) subtherapeutic, (2) therapeutic and (3) supratherapeutic, and treatment duration is up to 3 months. The light blue surface is studied by means of dose-ranging, short-time trials, and areas planned to be investigated in the phase III programme are contained within bold lines (up to 3 months). Spontaneous reports, represented by the black arrows, are used to obtain information on the effects of short- and long-term administration of supratherapeutic doses.

confounding by indication is less likely to be a problem in observational studies.

3.3 Drug C

Drug C is a non-peptide, vasopressin-2 agonist intended for the treatment of nocturnal enuresis in children and nocturia in the elderly. In comparison with orally administered desmopressin, which is a synthetic peptide vasopressin analogue currently used for these indications, higher and less variable bioavailability is expected to confer an improved safety profile. Hyponatraemia is a rare but serious adverse effect associated with the use of desmopressin.[14,15] Since drug C has a similar mechanism of action, an increased risk of hyponatraemia seems probable. With respect to its planned use for the treatment of nocturia in elderly patients, who often take concomitant drugs, the management of potential interactions would be a key concern. In particular, in light of their use in this group of patients, concomitant use of cyclo-oxygenase inhibitors would be a concern in relation to the risk of hyponatraemia. Theoretically, enhancement of the antidiuretic effect of drug C and an increased risk of hyponatraemia would be expected.[16] The risk could be avoided if such patients were excluded from

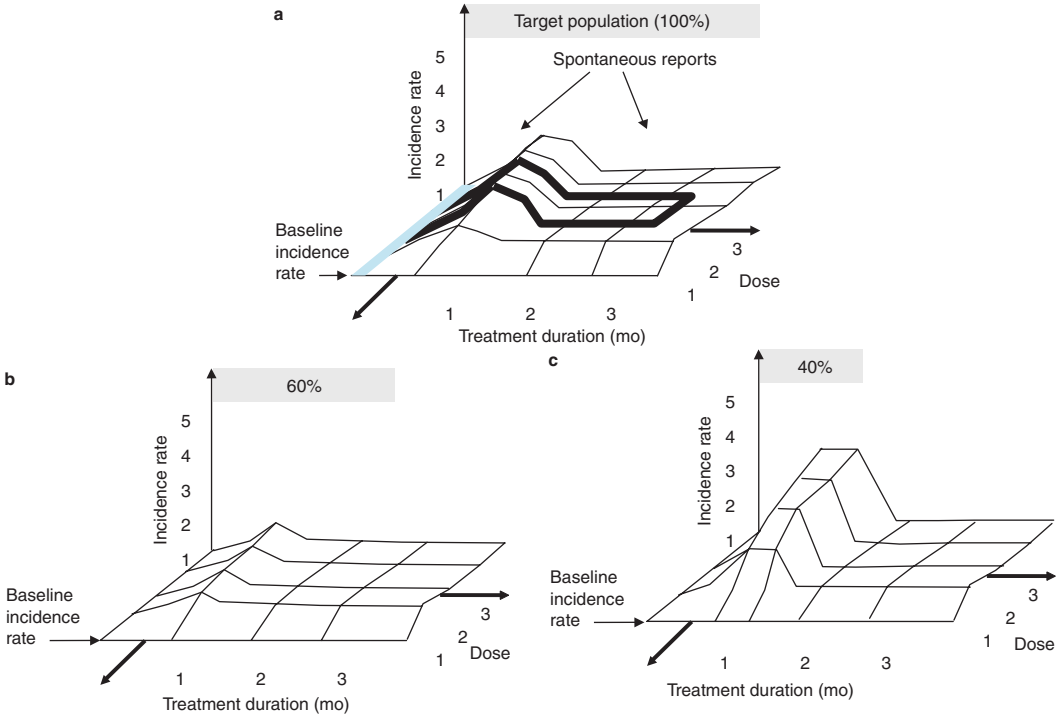

Fig. 4. Dose, time, susceptability (DoTS) graphs for drug C, a non-peptide, vasopressin-2 agonist intended for the treatment of nocturnal enuresis in children and nocturia in the elderly. The assumed incidence rate of hyponatraemia in elderly patients (arbitrary units), in relation to dose and treatment duration, is shown for (**a**) the overall target population, (**b**) the subgroups of patients not receiving cyclo-oxygenase inhibitors and (**c**) those receiving cyclo-oxygenase inhibitors. The baseline incidence rates of hyponatraemia do not differ between the two subgroups (**b** and **c**). Doses are (1) subtherapeutic, (2) therapeutic and (3) supratherapeutic, and treatment duration is up to 3 months. The light blue surface is studied by means of dose-ranging, short-time trials, and areas planned to be investigated in the phase III programme are contained within bold lines (up to 3 months). Spontaneous reports, represented by the black arrows, are used to obtain information on the effects of short- and long-term administration of supratherapeutic doses.

phase III trials. However, this should lead to a label contraindicating concomitant use and a significantly reduced target population (figure 4b–c). Alternatively, the possibility of precautionary concomitant use could be investigated. Based on previous experience with desmopressin-associated hyponatraemia in elderly patients,[14,17-20] a possible scenario is presented in figure 4. Based on the DoTS terminology, hyponatraemia caused by drug C could be classified as a collateral effect occurring at an intermediate stage, with a drug interaction as one source of susceptibility.

With respect to the baseline incidence, clinically significant hyponatraemia is not rare in elderly patients. Previous experience with desmopressin in elderly patients suggests that treatment with a vasopressin-2 agonist is likely to be associated with peak incidence of hyponatraemia within the first 3 weeks, and then be followed by a moderately increased risk in those who 'survive' the first critical period.[17-19] Given the relatively short induction time and the relatively high baseline incidence rate of various degrees of hyponatraemia, it would be reasonable to assume that much information on the combined use of drug C and a cyclo-oxygenase (COX) inhibitor could come from phase III trials (the area within bold lines). In order to study concomitant use, the recruitment strategy could be either passive (not excluding patients using COX inhibitors) or active

(actively including such patients). In the subsequent analysis, the relations between the surfaces in figures 4b and 4c would be of interest. It would be important to assess to what extent concomitant use increased the relative risk or changed the induction time or dose dependency of hyponatraemia. These aspects would all affect the decision to advise concomitant use with increased monitoring of sodium, or to contraindicate treatment all together.

Obviously, information from phase III studies would have to be supplemented with data from interaction studies in relevant patients. If a decision is finally made to launch the product with a label permitting concomitant use, a postmarketing strategy would have to be conceived to deal with this expected reaction. Clinically significant hyponatraemia in the elderly often results in an emergency room visit and hospitalisation. Thus, if possible, studies in hospital registries should be performed in order to estimate the incidence rate and to assess whether it was acceptable. Based on the mechanism of action, only current exposure would be of interest. In this case, since the reaction is well known, spontaneous reports would provide information on risk factors for hyponatraemia rather than generate a signal.

4. Discussion

In the process of conceiving a pharmacovigilance plan, as proposed in the ICH E2E guideline, the challenge will be how to address issues appearing in the safety specification with a set of appropriate pharmacovigilance methods. For successful planning, the various, and sometimes complex, dimensions of the adverse reaction in question have to be appropriately described. Since these dimensions can be visualised with DoTS graphs, this approach offers a way of depicting and analysing the relevance of an adverse reaction. In particular, the clear representation of time course should be of relevance for study design.

A model, such as a DoTS graph, is a human construct of the most important aspects of a part of a complex reality.[21] The modelling process involves abstracting, with the intention of focusing selectively on these central aspects. After having attained a certain level of refinement, an abstraction, or a combination of abstractions, is used to create a model. In pharmacokinetic and pharmacodynamic analysis in the early stages of drug development, modelling is extensively used to describe, explain and predict.[22] For example, three-dimensional response surface modelling is increasingly being used to illustrate pharmacodynamic drug-drug interactions.[23] Clearly, if a significant number of adverse reactions and co-variates (i.e. susceptibilities) were considered in the modelling process of the safety profile of a drug, an overwhelming amount of data and work would be needed to draw all possible DoTS graphs. Hence, efforts would reasonably have to be reserved for key safety issues, and stratification limited to the most important co-variates. Also, the first DoTS graphs would have to be outlined based on fairly limited data, and extrapolations would have to be made from premarketing data and information on similar drugs. However, the modelling process in itself would most likely increase the understanding of the adverse reaction, and assigning values to the various dimensions would make explicit assumptions and gaps in knowledge. Also, the emerging DoTS graphs could serve as a starting point for consultations regarding suitable pharmacovigilance methods, sampling strategies or risk management. As experience accumulated over time, the graphs would be modified, which is work that would be facilitated if suitable software could be made available. With respect to the three separate DoTS profiles presented in this article, the current approach to pharmacovigilance relies mainly on spontaneous reports and is fairly effective in identifying the type of reactions exemplified by drug B. However, the adverse reac-

tion profile represented by the DoTS graph for drug A remains a challenge to our systems.

In conclusion, the DoTS approach, with appropriate extensions, may offer better understanding of the dimensions of an adverse drug reaction, and consequently provide a better basis for pharmacovigilance planning.

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