IONIC AND NONIONIC CONTRAST AGENTS. A CONTRIBUTION BY WHO-ITA AND THE DRUG DOCUMENTATION AND INFORMATION CENTRE OF REGIONE MARCHE (°).

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Summary

This is the first work on ionic and nonionic contrast media on the data collected up to 1989, reconfirmed July 2010, in the WHO Data Bank of the International Drug Monitoring Programme, based at Uppsala University and funded by grants from the Swedish Crown and Government. WHO-ITA / ITA-OMS, the denomination approved by the WHO Assembly, has been authorized in 1989 to use these data as the Italian representative, through delegation by the Health Minister of Italy, the sixth founding member of the System and the first to adhere to the network for the International exchange of data on adverse reactions (ADR) and events related to ionic (5) and non-ionic (2) contrast agents employed in the then participating countries. The database is highly heterogeneous, collecting data reported spontaneously or by regulation, verified as well as non-verified, sometimes published in the international scientific literature as isolated reports. The cases of ADR and/or adverse events reported and added to the official WHO thesaurus are classified into the first 30 standardized subdivisions approved in the annual meetings of the participating countries, and, after normalization as percentages, they are presented and discussed here for the first time, as characteristic profiles of each drug product, before undergoing the original tests requested by the Italian Health Ministry on 13.1.1989 as part of a study entrusted to the Chair of Pharmacology of Ancona University, approved by the Scientific committee of the Study Centre of the same Ministry.

Key words: International WHO Drug monitoring; ionic and nonionic contrast agents

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The tasks of the Service, as listed in the local NHS (USL 12) deliberation no. 36, of 28.7.1988, encl. 20, corresponding to those set by the Superior Health Council, opinion of 26.1.1979 (see encl. 1), and approved during the EEC-WHO meeting of 2.12.1983 [1], include documentation and information on drugs, among which radiological contrast agents.
The question, discussed in various contributions [2-6], was again addressed in the Report of the V Regional Council Committee regarding bill no. 259, "Unitary management of economic relations with chemist's shops and development of the health service IS", presented on 28.9.1988 in relation to the obligations introduced by law no. 531 of 29.12.1987.
Proposals have been announced regarding art. 1 of law no. 256 of 7.8.1982, "Protocols for diagnostic imaging agents". These have been followed by diagnostic laboratory profiles drawn up by the Italian Association of Clinical Pathologists, using criteria aiming at a lower degree of "routine rigidity".

In 1979 the WHO regional office for Europe set up a work group on the use of medications [7], and the regional law no. 7 of 3.3.1982 has itself cited the connection with the WHO-ITA National Pharmacovigilance Centre (art. 27) in all aspects of drug research and documentation activities. Intensive, systematic, consistent, international record-linkage is among the aims, methods and results of the WHO-ITA collaborative coordination [8], structured in the framework of the Dis-Net (Drug Information System Distributed Network), which collects, processes, and updates current "exploratory" experimental and clinical pharmacology information [9], also including epidemiological and social data.
The 1989 annual meeting of the representatives of the centres participating in the WHO drug monitoring programme, held in Geneva, approved a broader diffusion of the data collected by the International Bank, to which WHO-ITA has provided a significant contribution. Italy is one of the six founders of an organization that now counts 30 members, and the Italian Centre was the first to adopt the international interactive network [10]. The Protocol is enclosed (encl. 2).

1. The ethical problem of choice and the containment of pharmaceutical expenditure

Physicians, in their expert, cautious and diligent action need to obtain the patient's consent also to prescriptions and diagnostic examinations. For such consent to be an explicit manifestation of will it must be voluntary (i.e. not coerced), informed on the basis of a clear and detailed explanation of justified procedures and of alternative treatment options, complete, and conscious through the knowledge of all benefits and risks.
In situations where a patient's life is at risk but cannot provide a valid consent, parental consent must be obtained. For minors, individuals with mental illnesses, and seniors whose consent is not valid, the guardian (often a close relative) must take the patient's place in the treatment contract and provide the consent, which is essential for any medical procedure.

In normal circumstances, consent to the medical treatment is provided by the patient, who bears the burden and has the privilege of balancing the potential damage against the hoped for benefit. Because the patient is a layperson, full information must be provided, particularly on different treatment options, the justification for the procedure chosen by the physician, and its risks compared with other options. Contraindications and side-effects must be fully disclosed, and the patient helped to understand, so that he/she can make an exhaustive assessment and decision. The physician thus has a dual responsibility: to ensure the selection of the most effective and safe treatment option and therefore of the most reasonable therapeutic risk. Consequently, the physician also needs to be alert to any adverse effect, so that any necessary measures can be adopted. In addition, the physician has a moral obligation towards the community, and must communicate his/her findings, or at least the original notes or those related to the more severe circumstances, to

a Pharmacovigilance Centre. Lack or incomplete description of these findings have the potential to delay the identification of new adverse effects and the adoption of suitable measures, and entail a responsibility for pointless suffering or unjustified deaths [11, 12].

It may be useful for physicians to keep records that can support their moral faultlessness and ability to face up to their responsibilities, and to be prepared to prove that their actions were in line with the most recent scientific knowledge. The selection of a given drug, which must always be justified, must also be convincing, because patients have a right to quality treatment.
The reader is referred to reference # 11 for the scientific and R&D aspects, where they are exhaustively discussed. Anyway, an automatic no fault insurance needs to be adopted as soon as possible to protect the possible victims. The issues raised by art. 9 bis of Legisl. Decree no. 443 of 30.10.1987, "Urgent measures in the healthcare sector", converted into law no. 531 of 29.12.1987, where the drug monitoring provisions also list physicians' obligations, have been addressed in a 1988 Editorial [13].
As regards the choice of diagnostic contrast media, given the clinical importance of their pharmacotoxicological effects, it has been specified that "in several cases the physician requesting the examination should discuss the issue with the radiologist and take part in the decision" [14].

Finally, physicians are involved in the reorganization introduced by Ministerial Decree of 11.7.1988 (G.U. no. 192 of 17.8.1988), creating an NHS information system (IS) directed at the "stringent control of healthcare expenditure as well as the assessment of treatment quality", which inspires also regional law no. 259, mentioned above.
Its various themes, recommendations and provisions are parts of the integrated "learning together, working together" approach described in the WHO Technical Report no. 769.

2. Contrast agents

The 5th revision of the WHO Model List of Essential Drugs, section 14.2 – "Radiological contrast media", includes iopanoic acid (oral agent for biliary examination), amidotrizoate, iohexol and iotroxate as examples of drugs that can serve as complementary alternatives to the second one, "in case of rare diseases or in exceptional circumstances". The 1989 *Informatore Farmaceutico*, excluding oral products — for cholecystography: iobenzamate, iocetamide, iopanoate and ipodate —lists under the current ATC VO4a classification, subgroups e-f, which are required in the form of acids or of sodium salts and/or meglumine (N-methylglucamine): amidotrizoate (diatrizoate), iocarmate, iodamide, iodoxamate, ioglicate, iohexol, iopamidol, iopromide, ioserate, ioxaglate, iotalamate, iotrol, iotroxate and ioxitalamate. The compounds are *ionic monomers*, water soluble, high-osmolality and low-viscosity (e.g. acetrizoate, diatrizoate, iodamide, ioglicate, ioserate, ioxitalamate, iotalamate and metrizoate); *ionic dimers* (iocarmate, iodipamide, iodoxamate, ioglycamate, ioxaglate, iotroxate), *nonionic monomers,* with relatively lower osmolality and greater viscosity (iohexol, iopamidol, iopromide, ioversol, metrizamide); and *nonionic dimers* (iodecol, iotasul, iotrol) [16].

Of the high-osmolality ionic media, the official national drug information body has first considered amidotrizoate and iodamide, and among non-ionic, low-osmolality agents iohexol and iopamidol. It concluded that whereas there did not seem to be substantial differences between the two groups in terms of the overall frequency of reports, the cases of fatal reactions to iopamidol seemed to be significantly less frequent [17].
Confining the present contribution to a preliminary, group examination of intravascular and myelographic iodinated contrast agents, derived from triiodobenzoic acid (VO4ae) and triiodo-ophthlamic acid (VO4af), and according to the international literature, the choice is however

mainly between ionic and the more recent non-ionic agents, and here is a brilliant fruit of Italian and all-European research. In the same context—and this is something which does not appear to be irrelevant at a time where healthcare investment and expenditure are being rethought, contained and rebalanced globally—widespread adoption of the latter would see the annual budget of a radiological laboratory in the USA soar from 150,000 US$ to 3 m US$ [18], and that of a local Italian NHS body (USL) [19] from 150 m lire to at least 1.5 billions.

3. Chemico-physical characteristics, documentation and chemotoxicity information

Local positive contrast agents depict body structures that on radiological examination present similar densities, the structures with lower kinematic viscosity attenuating the x-rays to a greater extent (viscosity/density), in direct relation to the iodine concentration stably bound to them. The traditional agents, which have been in use for at least 35 years, consist of solutions that dissociate into a radiopaque anion and a cation with equivalent oncotic (osmolar) effect. Monomers, which have 2 ions for each 3 iodine atoms in the anion, are defined as having a 3:2 ion ratio, or 1.5 (e.g. diatrizoate, iotalamate, metrizoate), whereas dimers, where two identical or similar triiodinated parts are combined into a single stable unit, exhibiting in solution 6 iodine atoms and 3 ions (one anion and 2 cations), have a 6:3 ion ratio equal to 2 (e.g. iodipamide).
They are used in highly concentrated solution, achieving plasma osmolalities up to eightfold the physiological value, which is one of the most frequently reported causes of toxicity.
In 1972 metrizamide, a monomeric nonionic agent, unstable and therefore provided in lyophilized form to prepare solutions as needed, was introduced. The iodine concentration being equal, its osmolality is about 1/3, because the molecule does not dissociate in aqueous solution and has a (nonionic) ratio of 3:1, equal to 3. This ratio is also shared by last-generation amide-replaced agents, both ionic monoacid dimers such as ioxaglate, and nonionic monomers such as iohexol and iopamidol, which are stable, withstand high temperatures, and therefore come in sterile phials in low-osmolality solutions [19-23].
Beside viscosity and osmolality—which are strongly concentration-dependent—and lipophilicity and cation content, other characteristics of the individual molecules have been correlated to biological and clinical toxicity. For instance, the monoacid dimer ioxaglate has lower osmolality and greater viscosity than iohexol; the latter, and all nonionic agents in general, enhance myocardial contractility, whereas ioxaglate reduces it, possibly due to its non-negligible ability to chelate calcium, etc. It should be noted that their pharmacokinetic properties (distribution, catabolism, albeit limited, and excretion) are usually non–linear and dose-dependent, making statistical evaluation quite difficult.

Now it has become clearer that radiological contrast agents are not inert, and that the clinical importance of their side-effects, always adverse, is greater in case of direct, largely foreseeable pharmacological effects, such that their knowledge allows prevention to avoid critical situations in patients with specific diseases undergoing known drug treatments. However, despite the unpredictable incidence, the knowledge of the presumable production mechanism can guide towards a rational treatment that can resolve the symptoms or reduce their severity.
The literature regarding the pathogenesis of the individual events and reactions is vast [22-25], and we will not address its overview or meta-analysis here. Besides the increasingly detailed ongoing study of the types of interaction of each molecule with structures and functions of individual patients, what is of interest here is rather to establish whether the overall profile of each product has been estimated at acceptable levels of significance, namely the validity of the spectral prevalence of the associated adverse reactions (ADR), according to the “exploratory” rather than the “analytical” approach adopted in this series of notes (Cf.: [9]).
Unfortunately, the percent differences in the estimates of the various complications can be subjected to statistics only when the use of the various drugs in preliminarily stratified groups of

patients is known; therefore, absolute and relative values of rough epidemiological batches, whose randomization is not programmed according to observational and experimental designs that are precisely specified for each drug and procedure, cannot be accepted.[1] When the (spontaneous, random) baseline incidence of ADR ranges from 1:100 to 1:10,000, and the minimum number of patients who may be exposed and the incidence estimate (Cf.: "risk policy") of ADR, whose occurrence can be associated to drugs, is 1:5,000, then the minimum number of potentially exposed patients rises from 67,400 to 3,225,000 [28]. This requires any detailed investigation to include the observation of very large patients samples, practically all those being treated.
Underreporting has been highlighted, and is especially alarming for new, nonionic agents [29]; comparison of data pools from observation periods with widely different durations is certainly incorrect, while the influence of sophisticated marketing practices [30, 31] is not to be ruled out, particularly in the healthcare organizations where such molecules are used [32].
However, while the basic problem remains unchanged, it is essential to underscore that current epidemiological trends show increased reporting of suspected, putative, or analytically proved common toxicity reactions to the more recent agents.
In fact, whereas the clinical and radiological quality of the new agents is admitted, though without a consensus operative protocol on doses and rates of administration, a better, general subjective comfort is noted, with a dramatic reported reduction in minor complications (e.g. local pain and heat). However, prospective randomized multicentre double-blind controlled studies of the effects that can be associated with fatalities and with severe clinical conditions (at least arrhythmias, hypotension, renal insufficiency, and unpredictable (and inevitable) anaphylactic and "anaphylactoid" reactions) have been urgently called for [20, 25-26, 32, 34]. These studies would clearly require the prior definition of the groups at greater risk, in order to establish priority guidelines for the use of the more pharmacologically and clinically effective and, where possible least expensive, agents.

The new agents have not in fact been proven to be less harmful [18], and there is no clear evidence with regard to which groups are at greater risk and where greater benefits can be obtained (e.g. in subjects of what age, with what degree of severity of heart, liver or kidney disease, or of haematological or anxiety syndromes [28]). In addition, for instance, the customary prevention or correction of dehydration before urography is not internationally validated [20]; the same applies to patients where an idiosyncratic anaphylactoid reaction is thought likely [20, 27, 32] and as general prevention in cases where glucocorticosteroids [35] — controversial [36] — and calcium antagonists (for renal toxicity [37]) have been recommended.
In addition, in intravenous (iv) pyelography the peak velocity of expiratory flow is unchanged [38], and differences in the processes that regulate coagulation and fibrinolysis in the more recent agents have been considered to have limited clinical significance [39]. A double-blind, randomized ventriculography trial has found similar haemodynamic effects of diatrizoate and iopamidol, concluding that their large-scale replacement is unwarranted [40]. Another randomized controlled study of heart catheterization has found no differences in the incidence of renal toxicity between patients treated with the two agents [41]. However, low-osmolality agents are not perfect. In animals they can significantly increase ventricular fibrillation, related to the low sodium content and, notably, there is a real likelihood of damage that can be misinterpreted as operating in complete safety [43].[2]

[1] Analysis of the 1984-1989 Medline literature highlights enormously discordant risk estimates for adverse and even fatal side-effects (e.g. "minor" 8.3%; "modest" 0.05%; "severe" 0.005; "fatal" 0.0025% [24, 26]; "slight" 45%; "moderate" 6%; "severe" 0.4% [27]. From 0.003 to 0.001for the total of the signalled reactions, and from 0.0001 to 0.00005 for deaths [17]).

[2] The Adverse Reaction Newsletter of 3/4. 10, 1988 reported that a review of cases of shock associated with administration of iohexol, ioxaglate. iopamidol and metrizamide has been carried out in Japan. The Adverse Reaction Committee has required reporting by the medical staff, emphasizing the possibility of shock also in patients having been administered low-osmolality agents.

To those upholding marketing strategies that hinge on the lower cost associated with ADR treatment, including the intervention of medico-legal specialists and insurers, it is objected that the argument has been rejected in a study [27].
Without any doubt, physicians are being forced to make decisions that involve economic aspects, to the extent — it has been written — that in case of excess expenditure they are required to justify their actions, and if these are found wanting, to be fined. In a less trivial way, one can no longer take responsibility for decisions of this kind.

Could the huge resources obtained from the replacement of expensive with less costly drugs be better employed?

4. Some updated data from the WHO Database

The profiles of the suspicious adverse reactions reported to the International Bank as of 10th May 1989 (confirmed 5th July 1989) are illustrated in Fig.1, sub A, B, C, in relation to seven frequently used drugs randomly selected among the more representative of the three common groups of ionic monomers (amidotrizoate, iodamide and iotalamate), ionic dimers (iodoxamate and ioxaglate), and nonionic monomers (iohexol and iopamidol).
For products available as such (iodamide) and/or for those available as acid or meglumine and/or sodium salts the number of individual and group reports has been indicated. The profiles reflect WHO system-organ disorder classes of ADR. The number and relative frequency the overall percent frequency of the 30 of some of the individual ADR, with different degrees of severity, is reported in Table 1. The other available products are not examined here, least of all the sum of their class profiles and the comparison of the incidence of the individual ADR, which are being classified according to well-established modelling and maximum likelihood methods (Cf.: [45]). The International Bank can be used to submit queries to the interactive network, including comparisons of the frequency and profiles of reports vs use, and the contribution of single countries with reference to the different periods when the drugs have been sold.
Incidentally, it should be noted that despite the conditions imposed to companies, the physicians themselves and the local NHS articulations, reports are still quite few in Italy. Here we have

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The Swedish National Drugs Board (Pharmaceuticals. Newsletter, 12, III, 8, 1988) recommended that the new low-osmolality preparations be used, if available, in the following situations:

- iv administration to children,
- individuals > 65 years of age, patients with heart disease or a history of oversensitivity or anaphylactic reactions;
- exceptionally high doses are required;
- in examinations requiring intra-arterial administration;
- for phlebography and pulmonary angiography.

The College of Physicians and Surgeons of Alberta, Canada, has established that "low-osmolality non-ionic contrast agents as approved by the Health Protection Branch, be used for diagnostic purposes" whenever available. In Italy, the SIRMN (Italian Association of Medical Radiology and Nuclear Medicine) has discussed the Health Ministry circulars nos. 81 (1985) and 64 (1979) and has reaffirmed the need to avoid decisions based solely on economic considerations. In such case patients, informed so as to obtain their consent, should decide once again to pay any difference, but such decisions belong to the regulatory Authority (which is responsible for withdrawing the products of higher risk), the hospital's administration, the forensic physician, the judge and finally the physician and the radiologist. It has however been stressed that adequate scientific data for expert evaluation, which the judge must acquire, are lacking (Ionici e non Ionici. I molteplici aspetti dei mezzi di contrasto. Aggiornamenti professionali continuativi, *8, ed*-A. Chiesa, Class Ed., Brescia, 1986. p. 65-72).

focused on the distinct trends of the various drug classes, although they share similar characteristics, which can orient the investigation into chemotoxicity mechanisms and lead to ask whether the initially predominant element is indeed the hyperosmolality.
In addition, there emerges a wide range of side-effects, from mild to fatal, with a not negligible and fairly similar incidence for ionic and non-ionic, monomeric or dimeric agents.
The comparison of these data underscores the value of the WHO system, if this were still needed, a system that has been developed by trained, ethically motivated professionals, and which has proved essential also for the body of information it has collected (and made available), providing orientation, receiving reports, raising alarms, but also enabling parallel traditional and formal investigations and sustaining coordinated international analyses. Its data will also be useful in addressing the urgent need for savings and conversion of pharmaceutical investment.

5. Recommendations for urgent epidemiological coordination

We emphasize once again the need for a broad structure for active, systematic, intensive collection of methodically assessed data from observational prospective and other studies, controlled according to case control and retrospective and prospective cohort methods, based on record linkage, conducted in the framework of the most prestigious international coordination in representation of the national research body, which will be able to continue to act independently of the commercial parties involved.

WHO-ITA, as the national reference centre for the WHO pharmacovigilance system today, and through the section of the Service in charge of Drug Documentation and Information, in agreement with the Pharmaceutical Services, mainly those of hospitals [46-47], can operate well in this field, as the Health Ministry has done in the field of drug addictions [48].
Wherever limited lists have been adopted, developed countries included, the training and audit programmes that have constituted their operative arm, adequately supplemented with information technology resources, have had significant impacts on treatment quality and cost [49].
While the authorities provide for the setting up of the above-mentioned structure, the following recommendations can apply at the regional level [32]:
a) avoid the systematic rejection of less expensive drugs, upholding of the right not to be subject to the diversified operations peculiar to marketing;

b) contribute to the implementation and observance of the protocols for the identification of high-risk patient groups, including possible pre-emptive pharmacological provisions. Carefully monitor any concomitant treatment with nephrotoxic drugs (aminoglycosides, amphotericin B, cyclosporine, etc) of patients for whom data are less abundant, such as infants and seniors, those with elevated serum creatinine, atopic dermatitis, or a history of allergy (especially to components of the same groups of organoiodinated agents); patients with diabetes, myeloma, haemoglobin disease, bronchial asthma, nephropathy, liver cirrhosis, recent heart infarction, ventricular arrhythmia, other heart problems, angina, and anxiety syndromes;

c) reduce the number of procedures requiring contrast agents in favour of other imaging modalities, without forgetting that, like the more traditional digital subtraction angiography and contrast-enhanced computerized tomography, similar problems also exist for magnetic resonance imaging, as do techniques, sometimes aggressive but always sophisticated, of commercial pressure through subliminal persuasion;

d) encourage competition (prices can change!) and observance of the conservative ethics of avoiding impure involvements of the well-known types, such as financing of Institutes, direct and/or for staff; contributions for meetings and congresses, including those held in serene faraway

places; subscriptions to journals; advances towards the setting up of offices and practices; contributions and assistance through a wide range of well-known foundations, bodies and associations to which all citizens already contribute if they are correctly taxed;

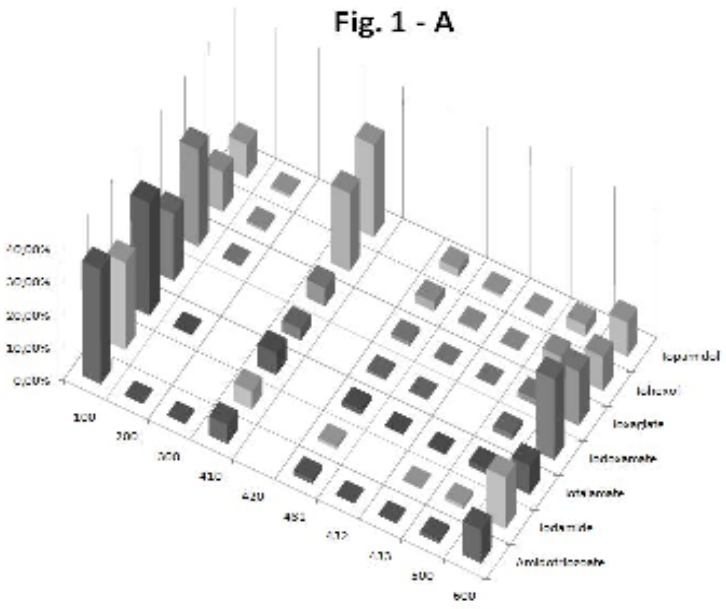
e) inform the patient of the dilemma of limited benefit obtained at a high cost.

There is no doubt that in a civilized and democratic society such as ours the informed public will be able to contribute effectively to the most appropriate choices.

Table of Fig. 1 – Seven products and their numbers of reports, total or for each n. 30 ordered WHO system-organ class disorders (SOCD) codes. Reports sent 5.7.2010 by Dr. Marie Lindquist, Director, VHO Uppsala Collaborating Center as per 1968-1989 years new PR22-2010 file.

		Amidotriozoate		Iodamide		Iotalamate		Iodoxamate		Ioxaglate		Iohexol		Iopamidol	
	CODE	26.017	%	659	%	7.251	%	452	%	1.568	%	2.396	%	2.053	%
1	100	9.082	34,91%	175	26,56%	2479	34,19%	92	20,35%	462	29,46%	292	12,19%	204	9,94%
2	200	48	0,18%			21	0,29%			3	0,19%	21	0,88%	18	0,88%
3	300	1	0,004%												
4	410	1.529	5,88%	36	5,46%	490	6,76%	16	3,54%	87	5,55%	572	23,87%	576	28,06%
5	420														
6	431	352	1,35%	6	0,91%	115	1,59%	4	0,88%	19	1,21%	67	2,80%	51	2,48%
7	432	23	0,09%			4	0,06%	2	0,44%	3	0,19%	16	0,67%	16	0,78%
8	433	14	0,05%	1	0,15%	3	0,04%			1	0,06%	9	0,38%	7	0,34%
9	500	313	1,20%	7	1,06%	116	1,60%	8	1,77%	29	1,85%	106	4,42%	73	3,56%
10	600	2.659	10,22%	103	15,63%	633	8,73%	111	24,56%	258	16,45%	249	10,39%	213	10,38%
11	700	15	0,06%			9	0,12%			3	0,19%	7	0,29%	1	0,05%
12	800	19	0,07%			4	0,06%			3	0,19%	4	0,17%	4	0,19%
13	900	5	0,02%			1	0,01%					2	0,08%		
14	1010	1.668	6,41%	62	9,41%	348	4,80%	32	7,08%	112	7,14%	109	4,55%	123	5,99%
15	1020	85	0,33%	2	0,30%	16	0,22%	2	0,44%	15	0,96%	25	1,04%	26	1,27%
16	1030	1.025	3,94%	27	4,10%	210	2,90%	18	3,98%	53	3,38%	74	3,09%	93	4,53%
17	1040	824	3,17%	9	1,37%	255	3,52%	10	2,21%	41	2,61%	79	3,30%	45	2,19%
18	1100	3.714	14,28%	127	19,27%	1163	16,04%	74	16,37%	177	11,29%	197	8,22%	205	9,99%
19	1210	7	0,03%											4	0,19%
20	1220	15	0,06%			6	0,08%			3	0,19%	7	0,29%	1	0,05%
21	1230	59	0,23%			25	0,34%			10	0,64%	22	0,92%	30	1,46%
22	1300	900	3,46%	8	1,21%	242	3,34%	11	2,43%	42	2,68%	58	2,42%	43	2,09%
23	1410	2	0,01%												
24	1420	3	0,01%			1	0,01%								
25	1500	4	0,02%												
26	1600														
27	1700	4	0,02%												
28	1810	3.402	13,08%	95	14,42%	957	13,20%	70	15,49%	242	15,43%	453	18,91%	315	15,34%
29	1820	232	0,89%	1	0,15%	144	1,99%	2	0,44%	3	0,19%	21	0,88%	4	0,19%
30	1830	13	0,05%			9	0,12%			2	0,13%	6	0,25%	1	0,05%

Fig. 1 - A



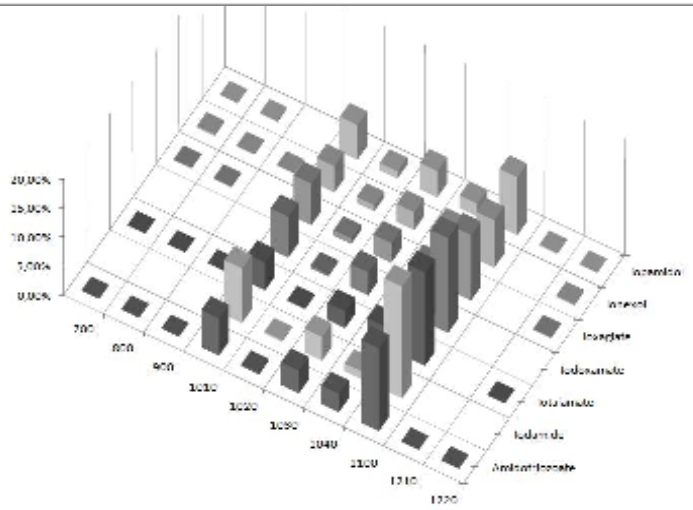


Fig. 1 - C

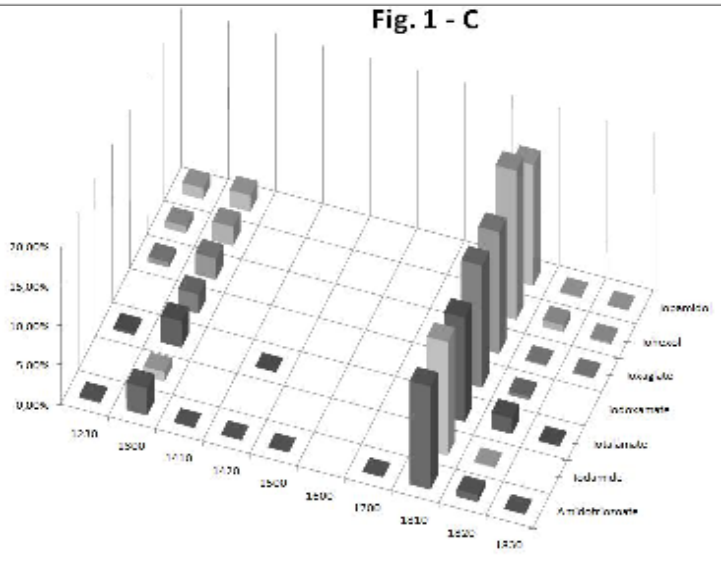
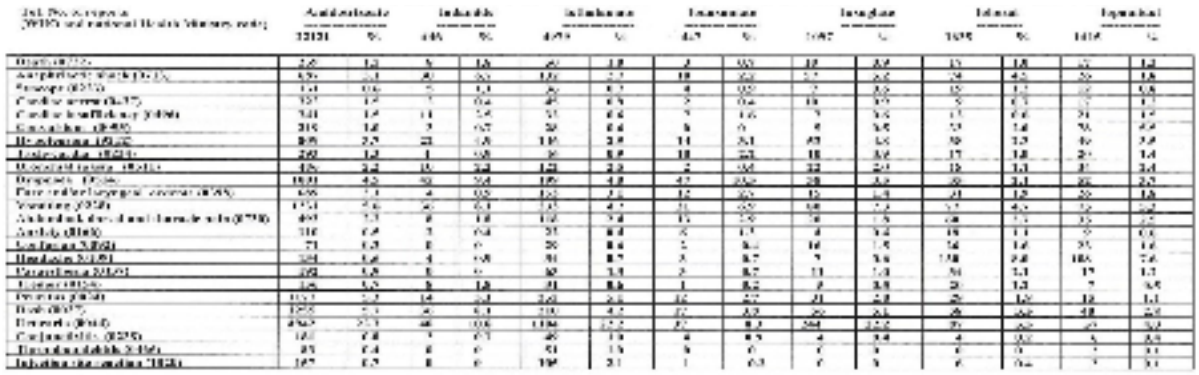


Fig. 1 - Profiles (A, B, C) each of 10 system-organ class disorders as indicated by their WHO-codes of 7 contrast agents (15 salts); y axis, percent number of n 40.396 Reports sent 10.7.2010 by Dr Marie Lindquist, Director, WHO Uppsala Collaborating Centre as per 1968-1989 years new PR22-2010 File, thus aggregated: 1 - Amidotrizoate - ATC VO8AA, 26.017 (acid, 12.541; meglumine amidotrizoate/sodium amidotrizoate, 13.457; meglumine amidotrizoate/sodium amidotrizoate/calcium amidotrizoate, 9; meglumine amidotrizoate/sodium amidotrizoate/iodine, 7; sodium amidotrizoate/lysine amidotrizoate, 3); 2 - Iodamide - ATC VO8AA, 659 (iodamide, 489; iodamide/iodamide meglumine, 6; iodine/iodamide meglumine, 157; meglumine/iodamide sodium, 7); 3 - Iotalamate - ATC VO8AA, 7.251 (acid, 6.945; iotalamate meglumine/iotalamate sodium, 306); 4 - Iodoxamate – ATC VO8AC, 452 (acid, 452); 5 – Ioxaglate – ATC VO8AB, 1.568 (ioxaglate meglumine/ioxaglate sodium, 1.568); 6 – Iohexol – ATC VO8AB, 2.396; 7 - Iopamidol – ATC VO8AB, 2.053. After the 5th meeting of the National Representatives (Portonovo di Ancona, Italy, 1982) the number of reports was corrected, for the Countries for which data are available, with the product use indices. Abscissas, 30 WHO system-organ class disorders (SOCD) and codes: 1- 0100, Skin and :appendages; 2 - 0200, Musculo-skeletal; 3 – 0300, Collagen; 4 – 0410, Central & peripheral nervous system; 5 – 0420, Autonomic nervous system; 6 – 0431, Vision; 7 – 0432, Hearing and vestibular; 8 – 0433, Special senses; 9 – 0500, Psychiatric; 10 – 0600, Gastrointestinal; 11 – 0700, Liver and biliary; 12 – 0800, Metabolic and nutritional; 13 – 0900, Endocrine; 14 – Cardiovascular, general; 15 – 1020, Myo-, endo-pericardial & valve; 16 – 1030, Heart rate and rhytm; 17 – 1040, Vascular (extracardiac); 18 – 1100, Respiratory; 19 – 1210, Red blood cell; 20 – 1220, White cell and RES; 21 – 1230, Platelet, bleeding & clotting; 22 – 1300, Urinary; 23 – 1410, Reproductive, male; 24 – 1420, Reproductive, female; 25 – 1500, Foetal; 26 – 1600, Neonatal and infancy; 27 – 1700, Neoplasms; 28 - 1810, Body as a whole, general; 29 – 1820, Application site; 30 – 1830, Resistance mechanism.

Table. 1 – Some adverse reactions (preferred terms) associated with the administration of the listed farmaceutical producs reported to the Uppsala WHO Center up to 10-5-1989.



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Encl. 1

The Italian Health Council (*Il Consiglio Superiore di Sanità*)

Was omitted

Considering that the following hospital functions are encompassed in the competence of Pharmacology and Toxicology:

- assistance to drug addicts* (law no. 685);
- monitoring of blood parameters in protracted drug treatments;
- pharmacotoxicological assistance in the wards that apply new experimental drug treatments;
- consultations concerning teratogenesis and abortion;
- participation in the drawing up of hospital therapeutic drug registers;
- collaboration with poison centres, ICUs, and dialysis wards;
- laboratory testing related to pharmacology (neurotransmitters, drugs, toxic agents and their metabolites, early toxicity markers, etc.)

expresses its favourable opinion…

Opinion of 26.1.1979 of Consiglio Superiore di Sanità*, approved and adopted by the EEC-WHO representatives in their joint meeting of 2.12.1983.*

**with specific reference to laboratory testing of drugs and toxic agents.*

Encl. 2

Information release by the WHO Collaborating Centre for International Drug Monitoring.
Protocol

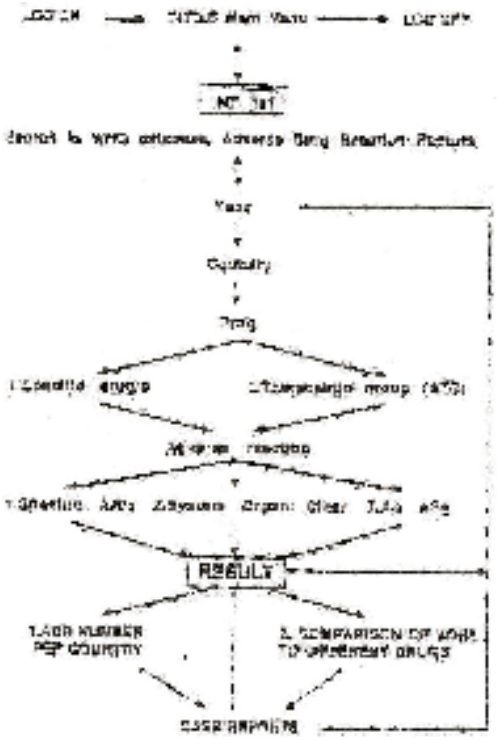
On the occasion of the September 1988 meeting of the National Centres in Uppsala, Sweden, it was agreed that ADR data would be provided to applicants according to a protocol, drawn up to avoid all interference with the rights of member countries to control their own data banks. The text below is the amended protocol, voted in the subsequent meeting (November 1989, Geneva, Switzerland).

The protocol is now being sent to all Collaborating Centres to provide guidelines on how to respond to queries.

1) Upon reception of a query all relevant reports shall be obtained from the data bank and sent to the National Centres that originally generated them;
2) Within two months (or less if all the information is available) of receiving the query, the WHO headquarters shall prepare a response based on the contribution of each National Centre involved. Four categories of responses by the National Centres are envisaged:

a) the National Centre allows the reports to be sent to the applicant. The reports are sent;
b) the National Centre formulates a comment or analysis of the reports, which is sent with the reports (or without them, as specified);
c) the National Centre does not reply within two months. The applicant is informed that the Centre holds information relevant to their request. No additional information is provided;
d) the National Centre does not allow the information it originally sent to be provided to the applicant. The latter is given neither the name of the Centre nor the information provided by it. The applicant is merely informed that «some data remain confidential on the behest of the National Centre from which they proceed» (neither Country nor Centre are identified).
3) Each applicant shall receive the caveat document (encl. 2.1) together with any reply that contains information from the WHO database.

Some National Centres are expected to agree to make sure that all information is released. They shall nonetheless be informed of the applicant's identity and of the relevant query, and shall not take initiatives unless by commenting on the reports within the two months deadline. The deadline is arbitrary and shall be discussed again at the next National Centres meeting, as will also be the general agreement protocol.



Encl. 2.1

Caveat document sent with the data released by the WHO Collaborating Centre

The Uppsala Collaborating Centre of the WHO Programme for International Drug Monitoring receives summaries of clinical reports of suspicious individual ADR to drugs from the National Centres of member Countries.
The Centre receives only limited information on each ADR.
It is important that the limitations and qualifications attached to such information and its use be clearly understood.
The term "pharmaceutical product" is used instead of "drug", to highlight the fact that the content in active or other ingredients of products marketed under generic or registered names can change over time and from place to place.
Reports, which are submitted to the National Centres, are produced spontaneously or under regulatory obligation. Some Centres accept reports only from medical practitioners, others from a wide range of health professionals. Some National Centres include the reports of the drug manufacturers in the information sent to the Collaborating Centre, whereas other do not.

The number of reports regarding a given pharmaceutical product can be affected by the spread of its use, by advertising, the nature of the ADR, and other factors that change over time and among products and Countries. In addition, no information is provided on the number of exposed individuals.
For these reasons the reports accepted by the National Centres vary widely in origin and proportion.
A number of National Centres contributing information to the Uppsala Collaborating Centre check the scope for a cause-effect relationship between administration of a pharmaceutical product and a suspicious ADR, whereas other Centres do not document this verification of the individual reports.

Processing time varies between Countries. The number of reports obtained by the Collaborating Centre can therefore differ from the number received directly from the National Centres. For these reasons the interpretation of ADR data, particularly those based on comparisons between pharmaceutical products, may be misleading. The information provided is not homogeneous in origin or in the criteria assessing the likelihood of a relationship between administration and ADR. Some Centres describe such information as "raw data". It should always be kept in mind that the utilization of such information is subject to this proviso.

Some National Centres that have authorized the release of their information recommend whoever intends to use it to contact them for their interpretation.

Total or partial publication of these data must be accompanied by specifications on:

- the origin of the data;
- the fact that they are not homogeneous, at least in terms of their origin or the likelihood that the pharmaceutical product caused the ADR;
- the caution that the information does not represent the WHO opinion.

Omission of these specifications can result in exclusion of the individual or the peripheral Organization responsible for the omission from obtaining additional information.

Encl. 3

February 1989. List of the National Centres participating in the WHO Pharmacovigilance Programme.

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