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SHORT COMMUNICATION

Pyrazinamide use as a method of estimating under-reporting of tuberculosis

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SUMMARY

OBJECTIVE: To develop a method of validating the notification of active tuberculosis by physicians in the Netherlands.

METHOD: The chemotherapeutic agent pyrazinamide was used as a marker for the occurrence of tuberculosis. On the basis of defined daily doses (DDD) of pyrazinamide dispensed to out-patients, an estimate was made of the number of patients with tuberculosis in the Netherlands in the period 1994–1998. DDD is a technical unit of measurement and does not necessarily reflect the recommended or actual dose used. Usually it is based on the average dosage per day for the main indication in adults with normal organ function. The Dutch Drug Information Project (GIP) of the Health Care Insurance Board (CVZ) provided the DDD data. Based on the notification of tuberculosis patients to the Netherlands Tuberculosis Register (NTR) we calculated how much pyrazinamide (measured in DDDs) these patients would have used depending on their body weight.

RESULTS: The number of DDDs prescribed according to the GIP pharmacy records differed by only 8% from the number of DDDs calculated on the basis of notification to the NTR; 6889 patients should have been registered instead of 6349.

CONCLUSION: The close correlation between the use of pyrazinamide as measured by the GIP and NTR provides strong evidence that in the Netherlands tuberculosis is reported in conformity with the guidelines for notifiable diseases. The method was simple to apply and may deserve follow-up in other countries.

KEY WORDS: DDD; pyrazinamide; tuberculosis; notifiable disease

IN THE NETHERLANDS, tuberculosis is a notifiable disease.[1,2] A case is notifiable when *Mycobacterium tuberculosis* complex is present in a patient's samples, or when a physician makes the diagnosis of tuberculosis on the basis of symptoms and clinical and radiological signs and decides to start curative treatment with anti-tuberculosis drugs. A medical microbiology laboratory or a treating physician is obliged by law to notify the Municipal Health Service in the region where the patient lives.

After receiving notification, the staff at the Municipal Health Service fill in registration forms for the Inspectorate of Health (IGZ) and for the Royal Netherlands Tuberculosis Association (KNCV), which keeps the Netherlands Tuberculosis Register (NTR). The register holds anonymous detailed information on every tuberculosis patient reported to the Municipal Health Service. After notification, the staff at the Municipal Health Service record the data for epidemiological purposes and start source and/or contact tracing. In addition, patients are monitored by a TB nurse from the Municipal Health Service to prevent resistance induction from treatment errors.

The number of patients with tuberculosis in the Netherlands is closely associated with the influx of persons from countries where tuberculosis is highly endemic. There are more extra-pulmonary forms of tuberculosis among these persons than among Dutch tuberculosis patients. In the case of non-infectious forms of tuberculosis, there is a greater risk of under-reporting by the treating physician, because there is no need for contact tracing. In addition, if the diagnosis has not been confirmed bacteriologically, the laboratory cannot notify the Municipal Health Service.

To estimate under-reporting, this study compared the number of days of pyrazinamide (PZA) use registered by the NTR with the number of days of PZA use measured on the basis of data from the Dutch Drug Information Project (GIP) of the Health Insurance Board (CVZ) during the period 1994–1998. Pyrazinamide was chosen as a marker for tuberculosis because this medication is used solely for the treat-

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ment of tuberculosis and it also usually forms part of the treatment regimen.[3–5]

MATERIAL AND METHODS

The use of pyrazinamide derived from notification to the NTR was compared to the quantity of PZA supplied on prescription by Dutch pharmacies. As the NTR has been computer automated since 1993, we chose the period from 1994 to 1998 inclusive for this study.

In the NTR the following patient data are included: age, number of days of hospitalisation and number of days of medication, including isoniazid, rifampicin, pyrazinamide or other anti-tuberculosis drugs.

The standard treatment of tuberculosis is a 6-month regimen consisting of daily isoniazid, rifampin, pyrazinamide and ethambutol given for 2 months followed by isoniazid and rifampin for 4 months. Pyrazinamide is always given for at least 2 months, but is continued after this period if no sputum conversion has occurred. Treatment with pyrazinamide can also be continued after 2 months if the final typing and resistance pattern have not been determined yet, pending the results of the cultures.

In the Netherlands the recommended dosage of pyrazinamide is 30 mg/kg body weight per day, with a maximum of 2 g per day for 2 months.

Data on the out-patient use of PZA were made available by the GIP over this period. PZA use was calculated as the number of defined daily doses (DDD) per year. DDD is a technical unit of measurement and does not necessarily reflect the recommended or actual dose used. It is usually based on the average dosage per day for the main indication in adults with normal organ function.[6–9] On the basis of population data from the GIP and the total Dutch population, an estimate was made of the number of patients with tuberculosis throughout the Netherlands.

According to the World Health Organization (WHO), the DDD of PZA is 1500 mg per day.[5] The actual dosage prescribed (prescribed daily dose, PDD) may deviate, for example on the basis of the patient's weight. Therefore, a correction factor was determined. Distinction was made between patients aged under 16 years and 16 years or more, because children under 16 years usually weigh 50 kg or less. That means that for children aged <16, 1 DDD = 1500 mg PZA/day is prescribed and that for patients $\geqslant 16$ years 2000 mg PZA/day is prescribed. In the Netherlands tuberculosis patients $\geqslant 16$ years usually weigh more than 60 kg. A survey held by the first author among 36 tuberculosis physicians at the Municipal Health Services revealed that a dose of 2 g of PZA is prescribed for the majority of patients. A survey of tuberculosis patients' medical files at the Municipal Health Services in Nijmegen showed that in the period 1994–1998, 60% (100/163) of the patients received prescriptions for 2 g of PZA. It was assumed that in at least 60% of adult patients, PDD = 1.3333 DDD, and that for 40% of adults and for children aged <16 years the PDD = 1 DDD.

In the NTR, selection was made of days of PZA use on an out-patient basis, excluding the number of days during which the patient was hospitalised.

RESULTS

The following data were extracted from the NTR: during the period 1994–1998, 6349 patients were registered with tuberculosis in the Netherlands; 58% were not of Dutch origin. Pulmonary tuberculosis was present in 60%, extra-pulmonary tuberculosis in 33% and a combination of pulmonary and extra-pulmonary tuberculosis in 7%. Diagnosis of pulmonary tuberculosis was confirmed bacteriologically in 77% of the patients using Löwenstein Jensen (LJ) medium for culture; Ziehl-Neelsen stain (ZN) was positive in 21%. Extra-pulmonary forms were confirmed bacteriologically in 74% on LJ medium, while ZN was positive in 2%. Combined pulmonary and extra-pulmonary forms were confirmed bacteriologically in 82%, while ZN was positive in 16%.

The number of days of PZA use is reported in Part 3 of the NTR form, which had been filled in for 93.3% of the cases: the 6349 tuberculosis patients had been treated with PZA for a total of 623 070 days (Table). Correction for 100% completion of Part 3 led to 663 546 days of PZA in the 6349 patients.

According to the GIP, 854 288 DDDs had been supplied (Table). According to Dutch regulations, drugs for chronic diseases, like pyrazinamide, can only be prescribed for a maximum period of one month. By dividing the number of DDDs by the number of prescriptions, we found that the patients had received a 1-month supply of PZA per prescription on average, and that the PDD was equal to 1.3333 DDD (Table). This means that according to the GIP, PZA was dispensed for 640 732 days (854 288 ÷ 1.3333). The difference between the number of days of PZA use according to the NTR and the number according to the GIP was 4%.

If we assume that all of the patients aged <16 years and 40% of the patients $\geqslant 16$ years took 1 DDD PZA per day, and that 60% of the patients aged $\geqslant 16$ years took 1.3333 DDD PZA per day, then on the basis of the NTR data, the 6349 patients took 739 503 DDDs of PZA. After correction for 100% completion of Part 3, this means 787 543 DDDs. In this case, the difference between the number of days of PZA use according to the NTR and the GIP (854 288 DDDs) was 8%. According to the NTR, a patient used an average of 124 DDDs (787 543 ÷ 6349), while according to the GIP, 854 288 DDDs were dispensed (Table). This means that notification should have been received by the NTR for 6889 patients (854 288 DDDs ÷ 124 DDDs per patient). Thus, under-reporting was 8.5%.

Table Number of tuberculosis patients treated with anti-tuberculosis drugs including pyrazinamide (PZA). Duration in days according to 1994–1998 Netherlands Tuberculosis Register (NTR) data and calculated defined daily doses (DDD), compared with data on PZA use from the Dutch Drug Information Project (GIP) of the Health Care Insurance Board (CVZ)

	Year of diagnosis					
	1994	1995	1996	1997	1998	Total
No. of TB patients	1 396	1 258	1 404	1 256	1 035	6 349
Age and days of PZA use						
<16 years	8 070	8 805	8 905	8 908	6 162	40 850
⩾16 years	141 497	120 345	121 888	111 784	86 706	582 220
Treatment duration of PZA in days (all ages)	149 567	129 150	130 793	120 692	92 868	623 070
Percentage completed of Part 3 of the NTR form	96.2	92.5	97.6	96.5	86.5	93.9
No. of days of PZA after correction for 100% Part 3 completion						663 546
Corrected DDD based on body weight						
<16 years × 1 DDD	8 070	8 805	8 905	8 908	6 162	40 850
⩾16 years × 1.3333 DDD (60%)	113 195	96 274	97 508	89 425	69 363	465 765
⩾16 years × 1 DDD (40%)	56 599	48 138	48 755	44 714	34 682	232 888
Total DDD corrected for body weight	177 864	153 217	155 168	143 047	110 207	739 503
DDD corrected for body weight and after correction for 100% Part 3 (NTR) completion	184 889	165 640	158 984	148 235	127 407	787 543
Total no. of DDD PZA (GIP)	200 837	191 496	187 579	140 136	134 240	854 288
	108.6%	115.6%	118.0%	94.5%	105.4%	108.4%
No. of prescriptions	4 789	4 521	4 484	3 520	3 394	20 708
DDD per prescription	41.9	42.4	41.8	39.8	39.6	41.3

By dividing the number of days of PZA use according to the NTR by the number of tuberculosis patients, we found that each tuberculosis patient took PZA for an average of 105 days (663 546 days of Z ÷ 6349 tuberculosis patients).

DISCUSSION

Our study showed that using pyrazinamide as a marker for tuberculosis provided a valid estimate of the number of patients with tuberculosis in the Netherlands.[6–9] In this way, it was possible to investigate under-reporting of a notifiable disease by Dutch physicians. Choosing a period of several years automatically corrected for those patients who were diagnosed in the last few days of one year and actually started treatment on anti-tuberculosis drugs in the following year. In addition, the wide time frame covered any doses of PZA that might have been obtained but not used, and later given to patients without health insurance by tuberculosis physicians at the Municipal Health Services.

Our calculations showed that patients had taken PZA for an average of 3.5 months, instead of the minimum of 2 months recommended in the protocol. The NTR data from 1998 show that 53% (582/1090) of patients took PZA for 2 months, 19% (208/1090) for 3 months and 20% (218/1090) for more than 3 months. No information on the use of PZA is available for 19% (251/1341) of the patients. A possible explanation for the longer treatment period is that if the resistance pattern was still unknown at 2 months, PZA would have been continued while awaiting the results.

Although only a very small proportion of patients take their medication under the supervision of a TB nurse in the Netherlands, known as directly observed therapy (DOT), treatment compliance is monitored very thoroughly. A TB nurse visits patients regularly at home, and checks the prescription and that the correct medications have been dispensed by the pharmacy. The same TB nurse fills in the number of days of pyrazinamide use on the registration forms.

It is possible that the GIP gave an under-estimation of PZA use among asylum seekers in the Netherlands, because this group falls under the care of the agency for the reception of asylum seekers (COA). In the period 1994–1998, asylum seekers spent an average of 15 months under the care of the COA.[10] It is not clear whether asylum seekers have an increased tuberculosis risk compared to the other risk groups. In the period 1994–1998, 21% (1335/6349) of the tuberculosis patients were asylum seekers; 54% (723/1335) of them had been in the Netherlands for less than 2 years (source: NTR/KNCV).

Underestimation of pyrazinamide use as a result of discharge of patients from hospital with supplies of PZA was considered to be negligible, as hospitals in the Netherlands are budgeted, and patients probably only received sufficient medication for the first day. In

the period 1994–1998, it was not yet customary to use pyrazinamide as a prophylactic. Pyrazinamide use on the basis of the GIP data may have led to overestimation of the number of patients with active tuberculosis, because treatment is also started on the *suspicion* of tuberculosis, although culture might later show that the tuberculosis is caused by non-tuberculous mycobacteria.

CONCLUSION AND RECOMMENDATIONS

Based on the number of days of pyrazinamide use by patients with active tuberculosis, as reported on Part 3 of the NTR forms in the period 1994–1998, and based on data from the CVZ GIP on the number of DDD of pyrazinamide supplied to out-patients, it can be concluded that in the Netherlands there is only a small amount of under-reporting of the number of patients with tuberculosis. In addition, it can be concluded that TB nurses generally monitor and record treatment accurately. From an epidemiological point of view, employing data on pyrazinamide use proved to be a simple and satisfactory method of validating notification of tuberculosis patients. The method may also be suitable for validation purposes in other countries.

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RÉSUMÉ

OBJECTIF : Développer une méthode pour valider la déclaration des tuberculoses actives par les médecins aux Pays-Bas.

METHODE : L'agent chimiothérapique pyrazinamide a été utilisé comme marqueur de l'existence d'une tuberculose. Sur la base de doses quotidiennes définies (DDD) de pyrazinamide administrées à des patients externes, on a estimé le nombre de patients atteints de tuberculose aux Pays-Bas pendant la période 1994–1998. Les doses quotidiennes définies (DDD) sont une unité technique de mesure et ne reflètent pas nécessairement la dose recommandée ou effectivement utilisée. Habituellement, elle se base sur le dosage moyen quotidien pour l'indication principale chez les adultes à fonction organique normale. Les données DDD ont été fournies par le Projet Hollandais d'Information Médicamenteuse (GIP) de l'Office d'Assurance des Soins de Santé (CVZ). Sur la base des déclarations de patients tuberculeux au Registre National de la Tuberculose des Pays-Bas (NTR), nous avons calculé combien de pyrazinamide (mesuré en DDD) ces patients auraient utilisé en tenant compte de leur poids corporel.

RÉSULTATS : Le nombre de DDD prescrites selon les registres de pharmacie du GIP ne diffère que d'environ 8% du nombre de DDD calculées sur la base des déclarations au NTR : il aurait fallu enregistrer 6.889 patients au lieu de 6.349.

CONCLUSION : Les corrélations étroites entre l'utilisation de pyrazinamide mesurée au moyen du GIP et du NTR est une preuve solide qu'aux Pays-Bas la tuberculose est déclarée en conformité avec les directives pour les maladies à déclaration obligatoire. La méthode a été simple à appliquer et mérite peut-être d'être utilisée dans d'autres pays.

RESUMEN

OBJETIVOS : Desarrollar un método para validar la declaración de los casos de tuberculosis activa por los médicos de Holanda.

MÉTODO : El agente quimioterápico pirazinamida fue utilizado como marcador de la existencia de una tuberculosis. En base a las dosis diarias definidas (DDD) de pirazinamida administradas a pacientes ambulatorios, se estimó el número de pacientes con tuberculosis en Holanda

en el período 1994–1998. Las DDD son una unidad técnica de medición y no reflejan necesariamente las dosis recomendadas o efectivamente utilizadas. Habitualmente, ellas se basan en la dosificación promedio por día para la indicación principal en adultos con función orgánica normal. Los datos sobre DDD fueron proporcionados por el Proyecto Holandés de Información sobre los Medicamentos (GIP) de la Oficina de Seguros de Atención de Salud (CVZ). En base a las declaraciones de casos de tuberculosis al Registro Holandés de Tuberculosis (NTR) se calculó la cantidad de pirazinamida (medida en DDD) que se habría tenido que utilizar en estos pacientes, de acuerdo a su peso corporal.

RESULTADOS: El número de DDD prescrito según los registros de farmacia del GIP difiere sólo en un 8% del número de DDD calculado en base a las declaraciones al NTR : se tendrían que haber registrado 6.889 casos en lugar de 6.349.

CONCLUSIÓN: La correlación estrecha entre la utilización de pirazinamida medida por el GIP y por el NTR significa una fuerte evidencia que los casos de tuberculosis en Holanda son declarados en conformidad con las directrices de notificación de enfermedades de declaración obligatoria. La aplicación del método fue simple y quizás pueda servir en otros países.