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Study of association of concomitant diseases with chemotherapy tolerability in children with active tuberculosis: results of a retrospective cohort research

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Article received: 18.01.2016; **accepted for publication**: 26.04.2016.

Background*: It is known that concomitant diseases in adults with TB contribute to the development of intolerance to chemotherapy.* ***Objective****: Our aim was to examine the association of concomitant diseases in children with tuberculosis with TB treatment tolerability.* ***Methods****: Analyzing of the adverse events (AE) occurrence frequency in the background of the standard (RF Ministry of Health order № 109) treatment with anti-TB drugs in a continuous retrospective cohort research. AE were considered to be drug-induced hepatitis, gastritis, neurotoxic and allergic reactions.* ***Results****: The authors analyzed the results of treatment of 231 children with active TB at the age from 0 to 14 years, 186 (80.5%) of which had concomitant somatic diseases. On the background of anti-tuberculosis therapy in hospital, 69 (37%) children with concomitant diseases and 22 (49%) children of the comparison group (p = 0.200) had AE. Differences in the structure of AE between the groups were not found. The most common AE were drug-induced hepatitis: they occurred in 58 (25%) children. The risk of AE on the background of anti-TB therapy was lower among girls and higher during treatment with cycloserine and fluoroquinolones.* ***Conclusion****: Concomitant diseases in children with active TB are not associated with the development of AE on the background of the anti-TB drugs therapy.*
Keywords*: children, active tuberculosis, chemotherapy, intolerance, adverse events, concomitant diseases.*
(***For citation***: Romanova M.A., Mordyk A.V., Merko E.A., Leont'eva E.S. Study of association of concomitant diseases with chemotherapy tolerability in children with active tuberculosis: results of a retrospective cohort research. *Pediatric pharmacology*. 2016;13(2):95-100. (In Russ). doi: 10.15690/pf.v13i2.1549.)

RATIONALE

Today the intensity of the epidemiological situation around tuberculosis is decreasing [1, 2]. However, children can nevertheless be considered a risk group for the development of tuberculosis [5-7] due to the imperfectness of their immune and breathing systems, as well as a high prevalence of somatic and infectious pathologies [3, 4]. This is due to the fact that somatic pathology in children is regarded to be a risk factor for developing tuberculosis [7, 8]. Children with tuberculosis, being treated in specialized in-patient hospitals, as a rule receive massive specific therapy. This can lead to many adverse effects (AE) in response to medicines and increase the in-patient period of treatment [9, 10]. Accompanying pathology contributes to the intolerability to chemotherapy (demonstrated on adult patients) [9, 11]. The prevalence of AE as a result of chemotherapy fluctuates between 47 and 83% (depending on the patients' characteristics and treatment conditions); it is often hepatic- or gastro-toxic effects [13-15], in diabetes patients - hypoglycemic reactions [12]. An association between a concrete anti-tuberculosis preparation and an AE is seldom established. At the same time, there is published data concerning the development of medicinal hepatitis as a result of treating with rifampin and the cardiotoxicity of INH [16].
The aim of our study was to investigate the association between accompanying pathology and tolerance to anti-tuberculosis therapy in children with tuberculosis.

METHODS

Study plan

A general retrospective cohort research was conducted.

Compliance criteria

Inclusion criteria:

- confirmed active tuberculosis diagnosed подтвержденный диагноз активного туберкулеза;
- age 0 to 14 years.

Non-inclusion criteria: specific process at calcination stage without activity traces (III dispensary record group).

Data source

The anamnesis of all children who were hospitalized to the Special child tuberculosis clinical hospital of Omsk city over the period from 2011 to 2013, were analyzed.

Study outcomes

As the main study outcome we analyzed the frequency of AE in an in-patient hospital while treating child tuberculosis patients with chemotherapy according to standard conditions (Russian Ministry of Health order № 109) [17]. As AE we considered medicine-induced hepatitis, gastritis, neurotoxic and allergic reactions.

We additionally determined the structure of tuberculosis forms in children with accompanying pathology (somatic, infectious) and without it. We distinguished different classes of somatic pathology in children with AE, that appeared secondary to the usage of anti-tuberculosis preparations.

Methods of registering outcomes

Hepatotoxic reactions were registered based on an increase of transaminase activity beyond the upper norm limit in the biochemical blood analysis after the intake of anti-tuberculosis preparations. Gastro- and neurotoxic reactions were noted down according to records in the medical history. Allergic reactions were established based on the records in medical history and/or according to the level of eosinophilia (> 8%) in the medical blood analysis (given the absence of confirmed helminthism).

Ethical expertise

The study was approved by the Ethical committee of the Omsk State Medical Academy (protocol № 60 from 18 Mar 2014).

Statistical analysis

We did not calculate the necessary sample volume. The data was processed using the Biostat (Russia) statistical software package. The quantitative indexes were described using the median (25th and 75th percentiles). The quantitative attributes were compared using the Mann-Whitney criteria, qualitative attributes - using the χ^2 Pierson criteria; when the number of observations in a group was <5, the exact Fisher criteria was used. We used binary logistic regression to analyze the risk factors of AE development, the results were presented int he form of odds ratio (OR) and a 95% confidence interval (CI).

RESULTS

Data characteristics

From 2011 to 2013 458 children were admitted for in-patient treatment, out of which 231 children matched the inclusion criteria. Of those not included into the study, 87 (38,3%) patients were from 15 to 18 years of age, 91 (40,1%) had tuberculosis of doubtful activity, 49 (21,6%) refused treatment or violated the regime (left the hospital without permission).

Of those included into the study, 186 (80,5%) had accompanying pathologies, 45 (19,5%) - didn't. The groups were comparable by age — 102 (55%) girls and 22 (49%; p =0,581), and age — 8 (4; 12) and 7 (4; 9) years, correspondingly (p =0,293). 111 (60%) children with accompanying diseases and 24 (53%) children without them came from socially unadapted families (where parents were abusing alcohol, used strong narcotic substances, were in jail, children from poor or incomplete families, children from foster houses, children under wardship).

In the group with accompanying pathologies, blood circulation system diseases were diagnosed in 55 (30%), diseases of the digestive system — in 16 (9%), breathing organs — in 26 (14%), urogenital system — in 29 (16%), neuro-psychic sphere — in 48 (26%), bone and muscle system and connective tissue — in 46 (25%), skin — in 15 (8%), eyes — in 30 (16%), endocrine system — in 11 (6%) children. Infectious diseases and parasites were detected in 46 (25%), anemia — in 21 (11%) patients.

The structure of active clinical tuberculosis forms did not differ in children of the compared groups (table 1). Most of the patients were diagnosed with tuberculosis of the breathing organs, including tuberculosis of intrathoracic lymphatic nodes.

Table 1. The structure of clinical forms of active tuberculosis in children belongign to compared groups

Attributes	Accomanying pathology (+), abs. (%)	Сопутствующая патология (-), abs. (%)	p
Breathing organ tuberculosis	169 (91)	44 (98)	0,214
Intrathoracic lymphotic node tuberculosis	129 (69)	35 (78)	0,350
Ghon's complex	21 (11)	7 (16)	0,595
Focal tuberculosis	5 (3)	1 (2)	0,668
Infiltrative tuberculosis	8 (4)	1 (2)	0,448
Cheesy pneumonia	1 (1)	–	0,805
Pulmonary tuberculoma	3 (2)	–	0,520
Tubercular pleuritis	2 (1)	–	0,648
Extrapulmonary tuberculosis	5 (3)	–	0,335
Generalized tuberculosis	12 (6)	1 (2)	0,240

There was no difference in the frequency of using various anti-tuberculosis preparations at hospital for children with accompanying diseases and in the control group (table 2). Nearly all children were prescribed with isonicotinic acid hydrazide, rifampicin, pyrazinamide; 2/3 of patients received ethambutol, every third child received paraaminosalicylic acid; every 4th child received kanamycin and prothionamide.

Table 2. Anti-tuberculosis preparations, used at hospital for children in the compared groups.

Preparations	Accompanying pathology (+), abs. (%)	Accompanying pathology (-), abs. (%)	p
isonicotinic acid hydrazide	175 (94)	45 (100)	0,200
rifampicin	174 (94)	44 (98)	0,457
pyrazinamide	174 (94)	45 (100)	0,169
paraaminosalicylic acid	62 (33)	16 (36)	0,915

streptomycin	1 (1)	1 (2)	0,352
kanamycin	37 (20)	14 (31)	0,153
prothionamide	50 (27)	10 (22)	0,653
fluroquinolone	9 (5)	–	0,137
cycloserine	10 (5)	5 (11)	0,287
ethambutol	122 (66)	32 (71,1)	0,597

Main study results

We detected AE in 69 (37%) children with accompanying pathology and in 22 (49%) — without it (p =0,200). The AE structure did not differ between the compared groups (table 3). Medicine-induced hepatitis and allergic reactions were the most often registered - in 58 (25%) and 46 (20%) children respectively. Medicine-induced gastritis and neurotoxic reactions were rare - in 6 (3%) and 4 (2%) children respectively. Combined development of AE (≥2) was noted in 18 (26%) of patients with accompanying pathology and in 6 (27%) of controls (p =0,867).

Table 3. Structure of adverse effects while treating children in compared groups with anti-tuberculosis preparations.

Indexes	Accompanying diseases (+), n =186	Accompanying diseases (-), n =45	p
Medicine-induce hepatitis, abs. (%)	42 (23)	16 (36)	0,107
Allergic reactions, abs. (%)	36 (19)	10 (22)	0,823
Medicine-induced gastritis, abs. (%)	5 (3)	1 (2)	0,668
Neurotoxic reactions, abs. (%)	4 (2)	–	0,418

Additional study results

Analyzing the risks of AE development while treating with anti-tuberculosis therapy has shown the following (table 4). A relatively low risk was characteristic for girls — OR 2,59 (95% CI 1,50–4,45), a relatively high risk — for patients intaking fluoroquinolones — OR 5,75 (95% CI 1,17–28,33) — and cycloserine: OR 3,33 (95% CI 1,10–10,10). Endocrine pathology has no effect on AE development: OR 0,144 (95% CI 0,018–1,148).

Table 4. Analysis of factors connected with the development of adverse effects while treating tuberculosis children with chemotherapy at hospital

Index	AE(-), n =140	AE (+), n =91	p
Age, years, Me (25th; 75th percentile)	7,5 (3; 11)	8 (5; 10)	0,869
Girls, abs. (%)	88 (71)	36 (40)	0,001
Disadvantaged families, abs. (%)	93 (66)	62 (68)	0,900

Accompanying conditions (%):	22 (49)	69 (37)	0,200
- diseases of the blood circulation system	37 (26)	18 (20)	0,361
- diseases of the digestive system organs	9 (6)	7 (8)	0,917
- diseases of breathing organs	15 (11)	13 (14)	0,544
- anemia	13 (9)	8 (9)	0,915
- diseases of the urigenital system	20 (14)	9 (10)	0,434
- neuro-psychic diseases	29 (21)	19 (21)	0,892
- diseases of the bone-muscle system and connective tissue	32 (23)	14 (15)	0,222
- skin diseases	8 (6)	7 (8)	0,747
- endocrine system diseases	10 (7)	1 (1)	0,030
- eye diseases	18 (13)	12 (13)	0,899
- infectious diseases and parasites	33 (24)	12 (13)	0,076
Clinical tuberculosis forms, abs. (%):			
- tuberculosis of breathing organs	127 (91)	86 (95)	0,424
- Intrathoracic lymphotic node tuberculosis	98 (70)	66 (73)	0,791
- Ghon's complex	16 (11)	12 (13)	0,846
- Focal tuberculosis	4 (3)	2 (2)	0,557
- Infiltrative tuberculosis	6 (4)	3 (3)	0,497
- Cheesy pneumonia	-	1 (1)	0,394
- Pulmonary tuberculoma	3 (2)	-	0,221
- Tubercular pleuritis	-	2 (2)	0,154
- Extrapulmonary tuberculosis	4 (3)	1 (1)	0,345
- Generalized tuberculosis	9 (7)	4 (5)	0,365
Anti-tuberculosis preparations, abs. (%):			
- isonicotinic acid hydrazide	133 (95)	87 (96)	0,916
- rifampicin	130 (93)	88 (97)	0,344
- pyrazinamide	133 (95)	86 (95)	0,890
- paraaminosalicylic acid	45 (32)	33 (36)	0,614
- streptomycin	1 (1)	1 (1)	0,634
- kanamycin	25 (18)	26 (29)	0,079
- prothionamide	33 (24)	26 (29)	0,486
- fluroquinolone	2 (1)	7 (8)	0,0210
- cycloserine	5 (4)	10 (11)	0,026
- ethambutol	89 (64)	65 (71)	0,274

***Note**. AE (-) / (+)— child groups that did not develop AE (-) or developed them (+).*

DISCUSSION

Main study result summary

There was no connection established between accompanying diseases (somatic, infectious) and the risk of developing AE for children treated with chemotherapy against active tuberculosis. The most prevalent AE, arising secondary to anti-tuberculosis therapy, were medicine-induce hepatitis forms and allergic reactions. Girls have a lesser risk of developing AE, while patients treated with fluroquinolones and cycloserine have a higher risk.

Discussion of the main study result
The frequency of AE development in response to anti-tuberculosis therapy that has been established for the studied cohort of patients, corresponds with the data provided by E.S. Ovsyannikova (39%) [18], but is higher than the results of T.I. Morozova (18%) [16]. Our study also affirms that hepatotoxic reactions dominate in the AE structure [13, 14], while gastrotoxic reactions were quite rare, which contradicts with the data of some earlier studies [15].

In the absolute majority of cases (80.5%) children develop tuberculosis secondary to various accompanying pathologies. At the same time, according to our data, events of intolerance towards chemotherapy of tuberculosis happened equally often both in children with accompanying pathologies and without them.

The data we acquired contradicts the data acquired by other researchers with regard to the connection between accompanying pathology and the patients' tolerance towards chemotherapy of tuberculosis [9, 10]. In her studies, T.I. Morozova [22] established a connection between the presence of an accompanying pathology and the frequency of developing side effects, while A.V. Mordyk et al. [23] regarded accompanying diseases as a risk factor for developing AE secondary to chemotherapy of tuberculosis. In our study, children without accompanying pathology anti-tuberculosis preparations developed AE more often.

This study found that the probability of developing AE secondary to using anti-tuberculosis preparations is higher for boys than for girls. No data concerning the connection between AE development probability and sex has been established in the works studying the tolerance towards anti-tuberculosis chemotherapy in children of different sexes [18]. However, there is an indication in studies concerning chemotherapy tolerance in adults [10], that women develop AE secondary to tuberculosis chemotherapy more often. It is important to note that children with AE were intaking cycloserine and fluroquinolones more often. A higher frequency of developing AE secondary to the usage of reserve anti-tuberculosis preparations as compared to first-line treatment preparations had been already noted earlier [19]. Apart from that, it was established that the appearance of some AE secondary to the usage of fluroquinolones can depend on the children's age [20]. At the same time, the best tolerance to the preparations of this group was registered for young aged patients without pathologies accompanying tuberculosis [21].

Study limitations
When analyzing the treatment results, we did not take into account the dosage of anti-tuberculosis preparations - just the fact of them being prescribed.

CONCLUSION
Treating active tuberculosis children with chemotherapy is complicated by the development of AE in 39% of cases. In our study, the risk of developing AE secondary to anti-tuberculosis therapy was not associated with the presence of accompanying (somatic, infectious) pathology. At the same time, it has been established, that the risk of developing AE was lower for girls and higher for those who received cycloserine and fluroquinolones. Most often chemotherapy was complicated by the development of medicine-induced hepatitis forms and allergic reactions in the form of dermatitis and eosinophilia. In most cases we noted the development of one adverse effect for anti-tuberculosis preparations.

Source of financing
Not indicated.

Conflict of interest
The authors declared they have no competing interests to disclose.

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