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Role of chemotherapy of taeniasis in prevention of neurocysticercosis

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Abstract

Neurocysticercosis (NC) is a serious public health problem in *Taenia solium* endemic areas and in some immigrants and international travelers. A key intervention in preventing NC is elimination of taeniasis by chemotherapy. Currently, two safe and effective taenicides, namely niclosamide and praziquantel, are available. Both are on WHO Essential Drug list, but are often inaccessible in *T. solium* endemic areas. Natural remedies, still widely used in some endemic areas, are frequently carcinogenic or highly toxic and as such should be discontinued. Chemotherapeutic intervention to control *T. solium* taeniasis/cysticercosis, whilst theoretically feasible, has several practical obstacles. These include poor public awareness, problems with diagnosing *Taenia* carriers, poor availability of taenicides where needed and low priority afforded to the control of NC. These can be overcome, respectively, by effective health education, wider use of newly developed coproantigen tests, strengthening of health services infrastructure and essential drugs distribution, and increasing the priority given to prevention of NC, as a leading cause of epilepsy in *T. solium* endemic areas. Information is accumulating on rational approaches to population-based short-term chemotherapeutic control measures. These are: widely available modern diagnostic tools and taenicides, treatment of any case of taeniasis, confirmed or probable, focus-oriented chemotherapy, irrespective of *Taenia* species implicated, improved sanitation, cooperation of veterinary and medical services, linkage with programs against epilepsy and cooperation of better educated communities. Now, it remains to take an advantage of existing tools and experience.

Keywords: *Taenia solium*; Neurocysticercosis; Chemotherapy; Control measures

1. Introduction

Neurocysticercosis (NC) is still a serious public health problem in *Taenia solium* endemic areas in Central and Latin Americas, Africa and large parts of Asia, including China [1,2]. It has become increasingly important in the USA, where, since 1980, as many as 1494 cases of NC have been diagnosed [3]. In non-Islamic developing countries, NC is the major cause of late onset epilepsy, which seriously degrades human's activities, when not treated (Meinardi in Pawlowski et al. [4]). Neurocysticercosis is a preventable infection, but scientific interest has tended to focus more on the clinical aspects of this disease than on its prevention.

In mid-19th century, in Central Europe, NC was endemic at a rate comparable to the situation in some developing countries today. Without safe and effective taenicides being available, successful control of NC in Europe took several decades and it was achieved mainly by rigorous meat inspection, improved sanitation, better health education and higher living standards. Introduction of safe and effective taenicides in 1960s and 1970s has introduced the potential role of chemotherapy in control programs [4]. Some problems related to taking a practical advantage of these taenicides are discussed here.

2. From old natural remedies to modern synthetic taenicides

Treatment of taeniasis has been practiced since ancient times, mainly by natural remedies such as male fern extract (containing filicin), Kosso flowers (kosso-toxin similar to filicin), pumpkinseeds (containing cucurbitine), areca nuts (containing arecoline), pomegranate (containing pelleteriene) and several others. Recently, as many as 33 taenicides were reported to be contemporarily used in Ethiopia [5]. Since early 20th century, several synthetic drugs were tried such as thymol (1912), carbon tetrachloride (1931), hexylresorcinol (1932), quinine (1933), mepacrine (1947), dichlorophen (1956), bithionol (1962), mebendazole (1975) or antibiotics such as paromomycine (1967) or aminosidine (1979). These drugs

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were either poorly tolerated or less effective than the two standard taeniacidal drugs now available: niclosamide (1960) and praziquantel (1972) [6].

2.1. Experience with taenicides between 1952 and 1979 in Poland

My experience in the treatment of patients infected with *Taenia saginata* reflects somewhat the developments in taenicides in Central Europe in the second half of the 20th century. In treating hundreds of *T. saginata* carriers since 1952, male fern extract was used only sporadically, due to fatal cases of intoxication being reported. In the 1950s, there was no other choice in Poland than to try pumpkinseeds (163 patients were treated with 60–65% cure rate). The seeds were replaced in the late 1950s by atabrine or an acridine derivative—Acranil given per os (respectively, 44 and 89 patients treated with 42% and 88% cure rate). Later, metallic tin compounds became available (226 patients — 88% cured) but then discontinued after reports of toxicity [7]. Then the time "worm cure without tears" arrived when niclosamide was introduced in the 1960, followed by praziquantel a decade later. With these safe taenicides, a high cure rate, respectively 80% and 90%, was achieved in hundreds of *T. saginata* carriers; it is generally accepted that *T. saginata* tapeworm is more resistant to anthelmintics than *T. solium* [8].

2.2. Toxicity and carcinogenicity of natural taenicides

In Europe, in late 19th and early 20th century, the only popular taenicide was male fern extract, widely used, irrespective of its poor tolerability and toxicity. Since the 1950s, it has been banned after some papers were published showing frequent complications following the use of male fern extract. For example, in Western Germany, among 22,000 cases of taeniasis treated with male fern extract, 18 patients died and 71 others have lost vision [9].

Natural taenicides are still widely used e.g., 80% of the population in Ethiopia take a taenicide every year and drug intoxication is a serious problem there [5]. Kosso flowers, popular in Africa, are responsible for hepatocarcinoma, visual disturbance and blindness [5]. Similarly, areca nuts, commonly used in Asia, are implicated as a cause of hepatocarcinoma, oropharyngeal and oral cancer [10]. Further use of these taenicides should be discontinued where alternative safe and effective synthetic niclosamide and/or praziquantel are available.

Introduction of these modern drugs has reduced the interest of pharmaceutical industry in developing new taenicides from original synthetic substances or old natural remedies. Occasionally, some taenicidal activities are being found among novel antiparasitic drugs, e.g. nitazoxanide [11].

2.3. Problems related to niclosamide

Niclosamide is barely absorbed in the gastrointestinal tract and, therefore, it is active against intestinal tapeworms but not against tissue-located cysticerci [6]. From the outset, it was known that the efficacy of niclosamide was highly dependent on its particle size (<1 μm). Later, it was observed that some generic products are less effective than the original ones and that niclosamide may loose efficacy during storage, probably due to polymerisation of its active particles. The production of niclosamide was much reduced in 1990s, whilst praziquantel increasingly became the taenicide of choice since it was at least 5× cheaper per treatment. The interest in niclosamide may soon return since it has been recently shown to inhibit the replication of SARS corona viruses [12].

2.4. Problems related to praziquantel

Naturally dying or artificially damaged *T. solium* cysticerci can cause a local tissue inflammation resulting in brain oedema and thus turn asymptomatic cysticercosis (50% of the cases) into a symptomatic clinical form. This process can be accelerated by various factors, including the use of taenicides such as praziquantel, which is absorbed and partly pass the blood–brain barrier. In fact, possible induction of symptomatic NC by using a single dose of praziquantel has been reported [13]. This phenomenon is probably related to the individual variability of praziquantel concentration in serum and in brain tissue, but it is rare. Symptoms possibly related to activation of cysticercosis were observed in one person among 10,173 people treated with praziquantel in Ecuador [14]. No such cases were observed during mass treatment of schistosomiasis with larger doses of praziquantel in Africa. Therefore, the risk of inducing symptomatic cysticercosis, as an adverse effect of treatment with a single dose of praziquantel, cannot be a reason to limit the use of praziquantel in taeniasis, but should be rather accepted as a calculated infrequent "price to be paid" for treating a *T. solium* tapeworm carrier, being a potential source of NC. Praziquantel remains contraindicated in ocular cysticercosis at any dose.

Nevertheless, the dose of praziquantel, used as a taenicide, should be as low as possible (5 mg/kg b.w.) as a single dose, which is 1/5 of the minimal daily dose, given for 3–6 days in cutaneous cysticercosis and 1/10 of the minimal daily dose, given for 2 weeks in NC [15]. In a population intervention in Ecuador, *T. solium* tapeworms were evacuated after doses varying from 3.4 to 7.3 mg/kg b.w., mean of 5.3 mg/kg b.w. [14]. In a clinical study, as low dose as 2.5 mg/kg was found effective in the elimination of *T. saginata* tapeworms, which are supposed to be more resistant to chemotherapy than *T. solium* ones [8,16].

3. Aim and strategies of control of neurocysticercosis

Theoretically, wide scale use of safe and effective taenicides could make the control of *T. solium* taeniasis/cysticercosis both simple and feasible [17]. In practice, however, there remain several obstacles to the successful interventions by using chemotherapy in endemic areas. The most important are: discrepancy of opinions on the aim and concepts of the strategies of NC control, difficulties in diagnosing *T. solium*

carriers, limited availability of modern taenicides and low priority of the NC control among health decision makers.

3.1. Aim of control of taeniasis/cysticercosis

Recently the definitions of various preventive interventions were re-discussed [18]. It has been accepted that control means reduction of disease incidence, prevalence, morbidity and mortality to a locally acceptable level as a result of deliberate efforts. This is what is urgently needed in the prevention of NC. Elimination of infection was defined as a reduction to zero of the incidence of a specified infection in a defined geographical area. This will be very difficult to achieve with NC even in limited areas. Eradication is meant as a permanent reduction to zero the worldwide incidence of a specific infection. A decade ago, taeniasis/cysticercosis was a candidate for worldwide potential eradication [17] but now it is no longer considered as such because of the insufficient operational experience [18].

3.2. Concepts of strategies in control of NC

The major control principle is to accept that elimination of any case of taeniasis in humans will diminish the pool of *T. solium* tapeworms, the source of cysticercosis for other humans and pigs and should eventually push the parasite reproductive rate below one. Consequently, chemotherapy of taeniasis becomes an indispensable element of any control interventions [19–23]. This has to be supported by health education and wider availability of diagnostic tools. Interventions, which reduce pig cysticercosis, such as sanitation, pigs chemotherapy, vaccination, meat inspection are auxiliary measures, which may make a success of control by chemotherapy of the carriers quicker and more permanent. The decision, which auxiliary measure(s) have to be implemented, depends on local endemic situation and control abilities [4].

Two vertical strategies of the control measures were defined at a PAHO meeting in 1990 [23], namely a long-term and a short-term strategy. The long-term strategy, usually a nation-wide, is designed to act over decades and depends on steady improvements in the quality of medical and veterinary services, health education, economy and legislation. Its coordination requires an administrative body. A short-term strategy was developed to allow for local urgency and severity of NC problem in some regions. It is designed to act over years and in restricted areas and requires mobilization of local public health, medical and veterinary services. The third alternative strategy, recently suggested [4], is a horizontal approach by incorporation of simple control measures into the existing health services activities, by given them instructions and diagnostic and therapeutic control tools. Which strategy is accepted and how it would be implemented and monitored depends again on local endemic situation and local control abilities.

3.3. Diagnostic control tools

The diagnosis of *T. solium* carriers is one of the weakest points in implementation of a successful control. The diagnostic sensitivity of the traditional methods is low: questioning for expulsion a tapeworm – about 50%, finding tapeworm proglottids or *Taenia* spp. eggs in faeces – 30–50% each. Only the coproantigen tests offer the sensitivity close to 100%. It may not differentiate *T. solium* from other *Taenia* spp. but this is not a critical point because any tapeworm in humans deserves to be eliminated for medical or epidemiological reasons. The coproantigen tests are stable and can be easily distributed, stored and do not request any specific equipment to be performed (Allan in Pawlowski et al. [4]). Coproantigen tests may be very useful in diagnosing individual *Taenia* carriers in hospitals or as outpatients as well as in screened populations e.g., in rural areas or military units [24]. A cost of the test could be low at a larger scale production. However, their availability is limited as in endemic regions there are only a few specialised laboratories, which can undertake commercial production of such a test, in cooperation with and supervision of some existing scientific reference centers (Allan in Pawlowski et al. [4]).

3.4. Population-based versus focus-oriented chemotherapeutic interventions

Theoretical mathematical simulation models of population-based chemotherapy in *T. solium* endemic areas demonstrate that at least 11 runs of mass treatments are necessary to achieve a local eradication of *T. solium.* This is mainly due to poor treatment coverage, human migration and/or infected pigs and eggs in the environment acting as a reservoir of infection [25]. Experience with a single mass treatment of the population in endemic Andean areas in Ecuador was also not very encouraging [14]. However, these studies demonstrated the focality of taeniasis, later confirmed in several other studies. In the Andean region, where over 11,000 persons were treated in 26 localities, there were 5 localities without any *T. solium* carriers, 16 localities having 0.1% to 5.0% of population infected with *T. solium* and 5 localities with the prevalence of *T. solium* carriers between 7.1% and 21.1% [14]. Treatment of the whole population, eventually repeated, was fully justified only in the last group of localities.

On the base of the field experience, the definition of the *T. solium* foci, which deserve chemotherapy, was drawn up as follows [4,26].

In endemic rural areas a focus is
- a small locality with high percentage of cysticercotic pigs and
- a farm supplying cysticercotic pigs.

Both foci can be identified by in vivo or postslaughter pigs inspection by veterinarians.

In rural and urbanised areas, both in endemic and non-endemic regions, a *T. solium* focus is
- an epileptic patient (especially with a late epilepsy) and his or her household members,
- any case of detected or probable taeniasis. Both foci can be identified during the routine medical examination.

Standard definitions for confirmed, probable and suspected cases of *T. solium* taeniasis have been given in the WHO, OIE and FAO manual [4].

3.5. Availability of modern taenicides

The success of any control intervention by chemotherapy is dependent on availability of safe and effective taenicides, i.e. for focus-oriented interventions or for daily medical practice. Both niclosamide and praziquantel are on WHO Essential Drugs list but this does not automatically mean that they are available, where needed. This problem concerns not only taenicides, but many other drugs and has been highlighted as an issue in the Millennium Declaration Goals [27].

Two factors are important to ensure availability of taenicides: identification of geographical area endemic for taeniasis/cysticercosis and making use of existing infrastructure for taenicides distribution in these areas. There are several potential delivery systems: (1) governmental systems — supplying drugs to governmental health centres, especially those in the periphery; (2) non-governmental systems — mainly missionary hospitals, usually acting in distant areas; (3) the commercial sector-like pharmacies, retail shops and sales agents as taenicides should be sold at the lowest price if not given free; (4) social marketing — through community health workers, well trained and supervised by health staff, after having a community-accepted NC control strategy.

3.6. Priority of control of neurocysticercosis

Control of *T. solium* taeniasis/cysticercosis, was, for over a century, the domain of veterinarians. The time has come for medical services to be actively involved in controlling taeniasis in humans. However, taeniasis/cysticercosis has never attracted high levels of attention in medical curricula and practice, except amongst neurologists and neurosurgeons, who are very scarce in developing countries [28]. Only some research institutes and public health institutions in *T. solium* endemic areas are involved in one or the other aspect related to implementation of the *T. solium* control measures. *T. solium* control programs have been discussed by WHO several times, but it was only in 2004 that the problem has been brought to the attention of World Health Assembly, the forum for deciding about world health policy [4].

The recent Global Campaign against Epilepsy can contribute to the control of taeniasis, as epilepsy is common in people with NC and is also one of the forms of epilepsy, which can be prevented (Meinardi in Refs. [4,29,30]). General support is expected from the UN Millennium Declaration, endorsed by 189 countries in 2000, in which among 8 major goals, to be achieved by the year 2015, one (nr 6) is directly and another five (nr 1, 2, 3, 7, 8) indirectly related to the NC control [27]. Some sponsor agencies are supporting studies on the optimal control measures e.g., in Peru [4,27]. The interest of parasitological community in control of taeniasis is growing [27], but this is not yet sufficiently reflected in existing health promotion policies and activities. Mr Bill Gates, co-founder of the Bill and Melinda Gates Foundation, stated at the Word Health Assembly in Geneva that: “The world has to devote more thinking and funding to delivering interventions — not just discovering them” [31].

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