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REVIEW

Oxfendazole: a promising agent for the treatment and control of helminth infections in humans

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ABSTRACT

Introduction: Oxfendazole (methyl [5-(phenylsulphinyl)-1H benzimidazole-2-yl] carbamate) has a particularly long metabolic half-life in ruminants, and its metabolite fenbendazole also has anthelminthic action. A very limited number of drugs are available for the treatment of some zoonotic helminth infections, such as neurocysticercosis and echinococcosis. More recent work has expanded oxfendazole's nonclinical safety profile and demonstrated its safety and bioavailability in healthy human volunteers, thus advancing the possibility of a new and greatly needed option for antiparasitic treatment of geohelminths and tissue parasites.

Areas covered: The present article reviews evidence supporting the safety and efficacy of oxfendazole against both gut and tissue dwelling helminths in animals, as well as more recent safety and pharmacokinetic data supporting its potential for use in human parasitoses.

Expert commentary: The pharmacokinetics, safety, and wide spectrum of efficacy of oxfendazole are consistently demonstrated in intestinal helminth infections of animals as well as in tissue dwelling larval cestode and trematode infections in diverse animal species. Now supported by first-in-human safety and pharmacokinetic data, oxfendazole becomes a promising alternative to the limited portfolio of antiparasitic drugs available to treat helminthic diseases of humans.

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Oxfendazole; benzimidazoles; antiparasitic drugs; helminths; cysticercosis; hydatid disease; Peru

1. Introduction

Broad-spectrum anthelmintics comprise three main groups (benzimidazoles [BZs] and probenzimidazoles, imidazothiazoles and tetrahydropyrimidines, and avermectins and milbemycins); they are highly effective against the majority of roundworm species. Avermectins and milbemycins are active against certain ectoparasites (mites and lice), whereas BZs may also have activity against some trematode and cestode species. The majority of benzimidazole carbamate anthelminthics in veterinary and human clinical use were approved nearly 40 years ago. Despite their extensive use in treating soil transmitted helminths (STH) and other parasitic diseases, the BZ anthelminthics albendazole (ABZ) and mebendazole are far from perfect [1]. Their efficacy against some intestinal and systemic human helminth species is clearly suboptimal, and if submitted today would probably not receive approval for some label indications.

Taenia solium cysticercosis is a zoonotic disease, endemic in most developing countries. It is responsible for approximately 30% of epilepsy cases in humans and causes significant economic loss to subsistence farmers due to the condemnation of meat from infected pigs [2]. Working in *T. solium* control, our group identified oxfendazole (OXF, methyl [5-(phenylsulphinyl)-1H benzimidazole-2-yl] carbamate) (Figure 1) as a promising agent to treat porcine cysticercosis. OXF comprises a benzimidazole carbamate ring that is characteristic of this group of drugs, with a phenylsulphinyl substituent in position-5. OXF has a particularly long metabolic half-life in ruminants, and its metabolite fenbendazole also has anthelminthic action. A series of studies in pigs confirmed OXF efficacy, and additional studies in other animal models show that its wide spectrum of action may include both intestinal and tissue dwelling helminths.

A very limited number of treatments are available for the treatment of some zoonotic helminth infections in humans, such as neurocysticercosis and echinococcosis, and all available treatments for these diseases are less than ideal in terms of efficacy or safety, making them inappropriate for use in control programs. More recent work has expanded OXF's nonclinical safety profile [4] and demonstrated its safety and bioavailability in healthy human volunteers (NCT02234570, NCT03035760), thus advancing the possibility of a new and greatly needed option for antiparasitic treatment of geohelminths and tissue parasites.

The present article reviews evidence supporting the safety and efficacy of OXF against both gut and tissue dwelling helminths in animals, as well as more recent safety and pharmacokinetic data supporting its potential for use in human parasitoses.

1.1. OXF use in farm animals

Since their appearance in the early 1960s, benzimidazoles have undergone structural modifications, resulting in improved safety and a broader spectrum of activity. Approved for veterinary use as Synanthic®, OXF was first identified by Syntex Research, Palo Alto

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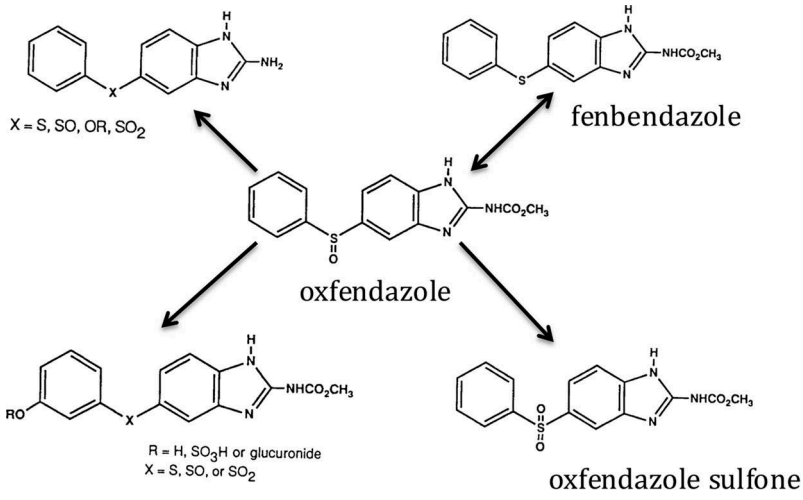

Figure 1. Metabolic scheme for oxfendazole in cattle and sheep [3].

as having anthelmintic properties against larval and adult gastrointestinal cestodes and nematodes in various animal species. OXF has been recommended as an additional strategy for control programs including giardiasis in dogs [5] and roundworms in horses and cattle [6]. Currently, OXF is approved in the U.S. as an over the counter medicine for use in cattle for the removal and control of several lung, stomach, and intestinal worms [7].

1.2. OXF in porcine cysticercosis

Several chemotherapeutic agents have been evaluated for the treatment of porcine cysticercosis. Early efforts with flubendazole were followed by evaluation of praziquantel (PZQ) administered at 50 mg/kg/day for 15 days. Variable efficacy was noted in these initial studies, and not all the cysts disappeared upon CT by day-47 after treatment. Later, 1-day treatment with PZQ (in three different doses of 25 mg/kg, 50 mg/kg, and 100 mg/kg) in three divided doses was reported to kill all cysts in 8 out of 18 pigs (44%) [8]. The efficacy of ABZ at a dose of 15 mg/kg daily for 30 days was reported in 1995 [9]. However, such a long regime is entirely inappropriate for use in field conditions. In the same year, a randomized trial by our group demonstrated that 3 days of ABZ at 30 mg/kg/day were necessary to destroy all cysts. A single dose of 50 mg/kg had some degree of efficacy, but animals presented marked side effects (extreme prostration, complete anorexia, and reluctance to move) and occasional mortality [9].

The efficacy, safety, and tolerability of a single dose of 30 mg/kg of OXF was demonstrated in controlled studies [10,11]. No viable cysts were found in the carcasses of eight animals treated with OXF (four with OXF alone, four receiving combined OXF and PZQ), in contrast to cysts into four untreated control animals. In four pigs treated with PZQ only, there was a decrease in the numbers of cysts, but those remaining were viable [10]. Other investigators have demonstrated similar 100% efficacy for muscle cysts but varying degrees of efficacy for brain cysts after a single dose of OXF [12].

1.2.1. Dose estimation

The dose of OXF (30 mg/kg) used in our initial pig study was calculated from previous experience with ABZ and may overestimate the amount of drug needed. A second study compared doses of 10, 20, and 30 mg/kg (single dose, $n = 6$ per group). After treatment, more than 75% of cysts in pigs from the control group (not treated) were viable, irrespective of their anatomical location. Again, no viable cysts were found in pigs treated with 30 mg/kg. In the 20 mg/kg group, there were viable muscle cysts in one pig and viable brain cysts in three, and most pigs in the 10 mg/kg group had surviving cysts. By the time of slaughtering (12 weeks after treatment), the carcasses of pigs treated with 30 mg/kg of OXF had a normal appearance, barely showing any signs of the resolved infection [11].

1.2.2. Time to cysticidal effect

The time for cysts to die and disappear after OXF administration is critical to the determination of the specific timing of treatment of infected pigs. A controlled study was designed to determine the time period between treatment and death of cysticerci. A clear decrease in viability and number of cysts was noted after the first week following treatment with OXF, though a few live cysticerci were still found in all tissues even at 4 weeks. Twelve weeks after OXF treatment, the meat examined was clear, and only minuscule scars were observed, except in one animal that had viable cysts in the brain. This study demonstrated that the death and destruction of cysticerci is caused not only by the direct effect of the drug or its residues but also enacted by the host's immune response over a period of time post-OXF treatment. Consequently, a period of 10–12 weeks would be required between OXF treatment and slaughtering to allow the pork to recover a suitable appearance [13].

1.2.3. Other comparative treatment studies

In 2012, our group reported a study in which 54 pigs naturally infected with cysticercosis were treated with seven antiparasitic regimes ($n = 6$ for each regime), steroids only (prednisone, $n = 6$), or untreated pigs ($n = 6$). OXF, ABZ, and the combination of ABZ plus PZQ were more efficacious that PZQ alone or nitazoxanide, and no effect was noted in pigs receiving prednisone only [14]. Longitudinal analyses of circulating parasite-specific antigen titers in 693 consecutive blood samples from 50 pigs from the above study, collected from baseline to

week 10 after treatment, showed that the decrease in antigen levels correlated well with the efficacy of treatment (inversely assessed as the numbers of the remaining viable cysts at necropsy), and confirmed the efficacy of the above listed regimes [15]..

In a comparative study aimed to assess the efficacy of triclabendazole, 18 naturally infected cysticercosis pigs were treated orally with triclabendazole (single dose, 30 mg/kg, n = 6), OXF (single dose, 30 mg/kg, n = 6), or placebo (control group, n = 6), and euthanized 17 weeks later. OXF-treated pigs had only degenerated cysts in their carcasses, whereas triclabendazole had very little effect [16].

1.2.4. OXF for the control of the transmission of cysticercosis

Prior to the use of OXF, treating porcine cysticercosis in field conditions was considered expensive and impractical because of the required multiple doses and duration of treatment. The efficacy of OXF when given in a single dose led us to include porcine chemotherapy in a field trial. An initial interventional study evaluated the effect of combined human and porcine mass chemotherapy as an innovative approach to the control of *T. solium* in 12 villages in the central Peruvian highlands. PZQ (5 mg/kg, single dose) was administered to the human population in the intervention areas to eliminate intestinal taeniasis, and OXF (30 mg/kg, two rounds) was administered to all pigs. The strategy was successful in the short-term, decreasing seroprevalence and seroincidence of specific antibodies in the porcine population. Benefits of the intervention as measured by incident cases of porcine cysticercosis remained statistically significant up to 16 months (P = 0.04). In this study, mass chemotherapy was effective in decreasing infection pressure in this hyperendemic area. However, the magnitude of the effect was small and did not attain the goal of eliminating transmission [17].

Another controlled study demonstrated that cysticercosis-infected pigs were protected from further cysticercosis infection for several months after having been treated with oxfendazole [18]. Considering that most pigs in field conditions live about 9 months, this study suggests that infected pigs would stop being a potential source of taeniasis infections after a round of OXF treatment. Obviously, other concomitant measures are still needed, since noninfected pigs still remain susceptible to infection.

OXF treatment of pigs was thus one of the measures used for our group to provide the first wide scale demonstration of the feasibility of eliminating *T. solium* transmission in an endemic region. In this study, transmission was interrupted in 104 out of 107 villages in rural Northern Coastal Peru, with a population of 80,000 inhabitants [19], and is now being applied in other endemic countries [20–22]. Recently, OXF has been approved for the treatment of *T. solium* infection in pigs [23,24].

1.3. Studies in other tissue larval helminthic infections (hydatid disease, fasciolasis, T. hydatigena)

In addition to the extensive work performed by our group and others in porcine cysticercosis, there is now evidence for high efficacy of OXF in other tissue helminthic infections, including echinococcosis, cysticercosis by *Taenia hydatigena* (cysticercus tenuicollis), and fasciolasis. Blanton et al. reported that OXF (four doses at weekly intervals) had significant efficacy against hydatid cysts in naturally infected sheep and goats [25]. Years later, a study from our group in 151 sheep naturally infected with hydatidosis (*Echinococcus granulosus*) demonstrated that animals treated weekly with 30 mg/kg of OXF (with or without nitazoxanide) had fewer fertile cysts, more degenerated cysts, and resulted in a higher efficacy against lung and liver cysts than sheep treated with two regimes of nitazoxanide or than the control group [26]. In a second study in 118 ewes, the same researchers confirmed similar efficacy for OXF administered alone or with PZQ, or for the combination of ABZ plus PZQ, in comparison with untreated animals [27]. In a masked, controlled study, our group has also demonstrated that a single oral dose of 30 mg/kg of OXF was fully effective against *Fasciola hepatica* in naturally infected sheep (n = 20) compared to no cure at all in untreated animals ($\underline{n}$ = 20); no side effects were discernible in the OXF-treated animals [28].

In a large necropsy study of pigs conducted in Northern Coastal Peru, we compared the prevalence of viable *T. hydatigena* metacestodes following treatment with a single dose of 30 mg/kg body weight of OXF (n = 506) or not treated (n = 142). Pigs were euthanized 6 months after treatment. Untreated pigs demonstrated a prevalence of *Cysticercus tenuicollis* of 27.5%, compared to only 2% in OXF-treated animals. The untreated group presented only viable cysts, whereas all the cysts in treated animals were already degenerated, with a thick membrane, turbid fluid contents and fibrosis. The study concluded that a single dose of OXF was effective against *C. tenuicollis*, thus providing an alternative drug for controlling this parasite in pigs [29].

1.4. Nonclinical toxicity studies

Toxicity studies conducted prior to the approval of Synanthic® for veterinary use included studies in rodents and dogs. The no observed effect level (NOEL) in single OXF dose studies was 1600 in dog, 3200 in rat, and 6400 mg/kg in mouse [7]. In 2-week toxicity studies conducted in rat at OXF doses of 11, 33, and 100 mg/kg, the following were observed: hepatocytic vacuolation (all doses); gastroenteropathy, decreased lymphoid, testicular, bone marrow activity (mid, high doses), and decreased hemoglobin and hematocrit (female, high dose). In dogs administered the same OXF doses for 2 weeks, decreased myeloid maturation in bone marrow and splenic lymphoid tissue and thymic atrophy were observed [7].

In 2-week toxicity studies conducted more recently in rat, the target organs of OXF toxicity were bone marrow, epididymis, liver, spleen, testis, and thymus. Toxic effects were observed at lower doses in female than in male rats; female rats had higher OXF exposure than did male rats [4]. During the recovery phase, decreased WBC levels returned to normal. Evaluated for potential behavioral or cardiovascular safety effects in dog, OXF did not provoke any signs of safety concerns [4].

Although many BZs are teratogenic in a variety of species, OXF seems to have a lower potential to produce reproductive effects. For example, in reproductive toxicology studies conducted as part of OXF approval as a veterinary medicine, OXF had no effects at reproductive endpoints whether administered to bulls or heifers, the latter before insemination as well as during pregnancy (including organogenesis) and 2 months of lactation. Additional studies

were conducted in the standard toxicology species (mouse, rat, and rabbit) [7]. Although OXF was fetotoxic in mouse and rat at very high doses, at therapeutically appropriate doses no fetotoxic or teratogenic effects were seen in mouse, rat, or rabbit. These findings are consistent with the absence of genetic toxicity seen in more recent studies [4].

1.5. Pharmacokinetics of OXF in animals

In studies in several ruminant and nonruminant species, orally administered OXF achieved significant levels in the plasma (see Table 1). Following the oral administration of 4.5 mg/kg OXF (Synanthic®) to cattle, OXF plasma levels peaked at 24–36 h post dose, remaining above the limit of detection for five days, and having a long plasma half-life, 20 h [30]. Another ruminant, sheep, had an OXF plasma half-life of 28 h.

However, long OXF plasma half-lives are not limited to ruminants, as our studies in pigs illustrate. We assessed OXF and its metabolites [(fenbendazole sulphone ($FBZSO_2$), fenbendazole (FBZ)] in plasma and tissue after administration of a single oral dose of 30 mg/kg OXF in 32 pigs; two different OXF formulations (n = 16 each) were evaluated. The main related moiety in plasma was OXF, with $AUC_{0\text{-}LOQ}$ of 210 and 160 h/µg/ml, and C_{max} of 5.4 and 3.8 0 ± 0.65 ug/ml for each of the formulations, respectively. The OXF plasma half-life was approximately 21 h, and the estimated posttreatment withdrawal time (time prior to meat being suitable for human consumption) was estimated to be 17 days [32].

In some other nonruminant species studied, OXF had somewhat shorter half-lives. In male rats, oral OXF doses of 15 and 60 mg/kg resulted in plasma AUC values of 35 and 88 h/µg/ml; the $T_{1/2}$ was 2.2 h at both doses. Plasma levels in female rats were significantly higher than in males (57 and 199 h/µg/ml, in male and female rats, respectively) [4]. In dog, an OXF dose of 50 mg/kg achieved an AUC of about 70 h/µg/ml and had a $T_{1/2}$ of approximately 5.5 h [33]. Although these studies did not calculate the oral bioavailability of OXF, they demonstrate that following its oral administration to numerous species, OXF achieves significant plasma levels (Table 1).

Since fenbendazole as well as most BZs are metabolized by CYP enzymes, it is likely that OXF is similarly metabolized; presently, no data in this regard are in the public domain. Neither have there been any investigations of potential drug/drug interactions through analysis of CYP profiles. Also we are unaware of any data on whether any of the downstream metabolites of OXF have been investigated for activity. By analogy with other BZs, the degradation metabolites do not have any activity, e.g. albendazole sulphone. Interestingly, only ABZ and FBZ have active metabolites, albendazole sulphoxide and oxfendazole, respectively, and both are sulfur containing. Fenbendazole, a prodrug of OXF, has good activity against a number of animal nematodes that are close relatives of human infecting species.

1.6. Human studies

A first-in-human single ascending dose (SAD) safety and pharmacokinetic study (NCT02234570) and the in-life portion of the multiple ascending dose safety and pharmacokinetic study (NCT03035760) of OXF administration to healthy volunteers have been completed. In neither case did safety concerns preclude administration of OXF across the planned oral dose range; rather, each study was completed as planned. A publication of the results of the SAD study is in preparation.

Oxfendazole, like most benzimidazoles, has a very broad spectrum of activity. Although no data exist for human-infecting nematode species *in vitro* or *in vivo*, OXF has an excellent profile against a wide range of animal-infecting intestinal nematode species. Good activity is therefore expected against the similar human gut nematode species. Recent studies, using validated *in vitro* and *in vivo* models of filarial infections that reflect likely macrofilaricidal activity in human filarial infections, have shown that oxfendazole has excellent oral activity which is comparable to flubendazole which, until now, has been considered to be the only BZ with macrofilaricidal activity [34–36]. Work toward a proof of concept OXF efficacy study (NCT03435718) in patients infected with *Trichuris trichiura* is underway.

Table 1. Pharmacokinetic data derived from oral oxfendazole administration to animals.

					Plasma analyte				
Gastric category	Species	Dose (mg/kg)	T_{max} (hours)	$T_{1/2}$ (hours)	Time relative to dosing	OXF (% or quantity)	OXF sulfone (% or quantity)	Fenbendazole (% or quantity)	% of oral dose absorbed/ % F
Multigastric (ruminant)	Cattle [3]	6	N.A.	20	24 h	43%	34%	23%	77/N.A.
	Cattle [3]	4.5*	N.A.	N.A.	24 h	241 ppb	76 ppb	97 ppb	N.A./N.A.
	Sheep [3]	6	N.A.	28	2 h/ 24 h/	70% 56%	8% 21%	22% 23%	85/N.A.
Monogastric (nonruminant)	Dog [31]	50	8	5.49	AUC_{last}	87% 70.9 h·µg/ml	13% 13.4 h·µg/ml	N.D.	N.A.
	Horse [3]	10	N.A.	26	AUC	14%	10%	77%	≪cattle or sheep/ N.A.
	Rat [3]	6	N.A.	NA	$AUC_{0\text{-}24\ h}$	29%	71%	<1%	100/N.A.
	Rat [4]	15	4	2.2(m) 3.1(f)	AUC_{last}	35(m), 57(f) h·µg/ml	N.A.	N.A.	N.A./ 33(m), 52(f)
	Rat [4]	60	5.3	2.2(m) 4.5(f)	AUC_{last}	88(m), 199(f) h·µg/ml	N.A.	N.A.	N.A./ 21(m), 47(f)
	Pig [32]	30	6.6	21.6	AUC	73% 209.9 h·µg/ml	26% 74.9 h·µg/ml	0.77% 2.20 h·µg/ml	N.A./N.A.

N.A. = data not available; ND = not determined
* data derived from intraruminal administration
% F = oral bioavailability; (m) = male, (f) = female

2. Expert commentary

The pharmacokinetics, safety, and broad spectrum of activity of oxfendazole have consistently been demonstrated in intestinal helminth infections of animals as well as in tissue dwelling larval cestodes (*Taenia solium* cysticercosis, echinococcosis, *T. hydatigena*), trematode (fasciolasis), and filarial infections in a wide range of animal models. Whilst animal models are an indication of potential activity in similar human infections, translating this information into human therapies is a significant challenge since the pharmacokinetics and metabolism are often very different. Thus, with each human infection it will be necessary to conduct specific studies to determine effective doses before moving into larger scale studies to register the product. For example, while OXF has been shown to be very effective in porcine cysticercosis, allowing single-dose treatment, the long half-life of OXF and ability to penetrate the brain parenchyma may not be seen with human infections. Similarly, when considering human intestinal nematode infections, it is not possible to directly associate effective doses in domestic species and it will be necessary to undertake dose ranging studies to determine regimens that are effective against the whole range of intestinal nematodes. One of the challenges is therefore to determine the infecting helminth species most likely to be amenable to treatment and to develop this first as a priority. This will in the longer term provide additional safety data to support further study in other infections.

Current data will probably be sufficient to support relatively short-term treatments for indications such as intestinal helminth infections, and we believe that there is probably sufficient additional data to allow longer durations that may be needed for indications such as echinococcosis. While the existing toxicological data may be adequate to allow a full program of development in a wide range of infections, it is possible that additional and potentially extensive work will be required to permit long term or repeat dosing. This would delay any work in the more problematic tissue infections that are currently poorly provided for in the therapeutic armory. However, supported by first-in-human safety and pharmacokinetic data, together with robust recent toxicology data, we believe that OXF is a promising alternative to the limited portfolio of antiparasitic drugs available to treat helminthic diseases of humans.

3. Five-year view

Further data are expected from a multiple-dose pharmacokinetic and confirmatory safety study, which is already under way. Early efficacy data from single- and multiple-dose Phase II studies should also be available during the next few years. This will be the result of a rolling program of proof of concept and early efficacy studies which will form the basis for a development program which will focus on the most amenable parasites. Given the time it takes to conduct and report studies, it is likely that the first evidence for a role for OXF will come from treatment of intestinal nematodes. This will focus on *Trichuris*, the species that is least well served by current therapies, while not ignoring the other species such as hookworm and *Ascaris* where current treatments are more effective. By the end of a 5-year period one might expect to see a full Phase III program for intestinal helminthiasis nearing completion, while larger scale studies in diseases such as echinococcosis, cysticercosis and filariasis will be beginning. As evidence of the safety and efficacy of OXF increases over this 5-year time-frame, we would hope that the first approvals will not be far off. However, in drug development, one cannot be too optimistic as many compounds fail either by not demonstrating the expected efficacy or by finding unexpected toxicities that stop development.

Key issues

- OXF is a benzimidazole with particularly long life in ruminants and some nonruminant species, efficacious for multiple helminthic diseases of animals.
- The nonclinical safety profile of OXF demonstrates its safety and bioavailability.
- OXF may provide a new option for antiparasitic treatment of geohelminths and tissue parasites.

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Declaration of interest

All authors are members of the Oxfendazole Development Group (https://oxfendazoledevelopmentgroup.org/), a nonprofit organization created to promote research and development of treatments for neglected tropical diseases. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

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