Currently Available Molluscicides

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Views about the importance of the role of molluscicides in the integrated control of human schistosomiasis have passed through cyclical changes over the past 15 years. For a time, it was hoped that chemotherapy alone would achieve significant morbidity control; it has since become clear that molluscicides cannot be easily excluded from the anti-schistosome armoury. In this review, Sheena Perrett and Phil Whitfield summarize the evidence for this conclusion and provide an overview of currently available synthetic molluscicides and those natural product molluscicides currently under active investigation.

In 1980, it was reported that numerous schistosomiasis control projects had shown that snail control by molluscicides, either alone or in combination with other methods, could be a rapid and efficient means of reducing or eliminating transmission. It was concluded that snail control procedures were to remain among the methods of choice for schistosomiasis control.

By 1985, the WHO reported changes in the priorities and operational approaches adopted in the control of schistosomiasis. Advances had occurred in parasitological diagnostic techniques and chemotherapy while programmes to eradicate schistosomiasis by multiple intervention techniques proved to be beyond the human and financial resources of most endemic countries. At this time, the aim became the control of morbidity due to schistosomiasis rather than the control of transmission. By the time of the most recent WHO technical report the consensus view had shifted perceptibly once again with some emphasis on the need for flexibility in control strategies and for transmission control.

Many recent studies have shown that control programmes based on chemotherapy alone can provide only temporary curtailment of schistosomiasis transmission. Other studies have shown that schistosomes have the potential to become resistant to praziquantel which is currently the drug of choice for the treatment of schistosomiasis. These results and the absence of an effective, safe schistosomiasis vaccine suggest that it is premature to dismiss molluscicides as an important factor in schistosomiasis control programmes.

Currently available synthetic molluscicides

No new molluscicide of any great significance has been developed in the past decade. Only one molluscicide, niclosamide, is widely used in control programmes. Three other synthetic molluscicides are reported to be in less extensive use; B-2 (sodium 2,5-dichloro-4-bromophenol) is used in Japan against Biomphalaria glabrata; copper sulphate is used in Egypt; and NaPCP (sodium pentachlorophenate) is used in China.

Both copper sulphate and NaPCP were in use in 1965 (Ref. 9). Copper sulphate, while an effective molluscicide in certain conditions, has a number of disadvantages: it is absorbed by soil and organic material, ineffective at a pH over 9 and toxic to many non-target organisms. There are also concerns about the safety of NaPCP: in 1965, it was thought to be potentially dangerous to the handler and has since been banned by the Japanese government due to environmental pollution.

A laboratory evaluation of the potential of the molluscicide B-2 for use in South Africa has shown promising molluscicidal activity, albeit not as high as that of niclosamide. The same study also showed that molluscidal levels of B-2 were harmful to populations of the indigenous fish, Oreochromis mossambicus. This is a serious problem because fish are often an important food source in areas where schistosomiasis is endemic.

Niclosamide (Fig. 1), a synthetic molecule first synthesised in 1964 (Ref. 9), and is still the molluscicide of choice. Niclosamide is highly active at all stages of the snail life cycle, killing 100% of Biomphalaria glabrata adults at concentrations as low as 1.5mg/l after a two-hour exposure, and B. glabrata egg masses at concentrations below 1mg/l after 24h (Ref. 14). Schistosoma mansoni larvae are immobilized and killed within minutes of exposure to niclosamide ethanolamine salt at a concentration of 0.3mg/l (Ref. 14). Niclosamide does not adversely affect any economically important crop plants, although certain algae and aquatic plants are damaged. Short-term studies on the toxicity of niclosamide in laboratory animals have shown that there are no cumulative toxic effects when the compound is administered either orally or cutaneously. In addition, some studies have been carried out with human volunteers receiving a single oral dose of 2000mg niclosamide and no adverse reactions were observed. The main drawbacks with niclosamide appear to be its high price and the fact that formulations cause high fish mortality at concentrations used to control snails.

In the use of biocides for disease control, there is a danger in relying on a small range of bioactive
compounds as target organisms can potentially develop heritable resistance. Niclosamide has been used since the 1960s and, although still highly effective, there have been some reports of increased tolerance among Bulinus truncatus in the field and in laboratory-reared B. glabrata. Although these indications have yet to cause serious difficulties in the field, there is clearly a need for new safe and effective molluscicides to be developed as an insurance against possible resistance.

In 1980, the development costs of a new molluscicide from initial laboratory trials to market availability were estimated at approximately US$10 million. Sixteen years later, this figure is likely to be much higher. New molluscicides are needed, but it is unlikely that the countries that most need them would be able to pay for their development.

The case for plant molluscicides

Much attention in recent years has been given to the study of plant molluscicides in the hope that they might provide cheap, locally produced, biodegradable and effective control agents in rural areas of developing countries where schistosomiasis is endemic. Some of the first attempts to control schistosomiasis by killing snails with plants were made in the 1930s (see, for example, Ref. 15). Since then, more than 1100 plant species have been screened for molluscicidal activity. In many cases, a systematic approach has been adopted in the search for molluscicidal plants based on ethnomedical uses.

In order to compare favourably with synthetic molluscicides, an alcoholic or lipophilic solvent extract of the plant should have an LC$_{50}$ towards target snails after 24 h at concentrations less than or equal to 20 $\mu$g ml$^{-1}$ at a defined water temperature. In addition, the plant should grow abundantly in the endemic area; regenerating parts (fruits, leaves and flowers) should be used avoiding the roots if possible so that the plant is not destroyed; application procedures should be simple and safe to the operator; the plant extract or molluscicide should possess low toxicity to non-target organisms (including humans); and costs should be low. It is clear that the probability of finding a ubiquitous molluscicidal plant that can be used in all endemic areas is small. Therefore, plant molluscicides must be chosen according to the local situation and native flora. Large numbers of plants have been found to have molluscicidal activity. This review will concentrate only on those that have been the subject of extensive study.

Ambrosia maritima is widely distributed in Senegal and is known to be molluscicidal with low toxicity to non-target organisms. The active compounds in the plant are thought to be sesquiterpenes. Field studies in the Senegal river basin were carried out using dried plant leaves. It was found that large amounts of crude plant material were required to achieve significant snail population reductions and it was concluded that A. maritima would be unlikely to be of use in schistosomiasis control programmes.

Triterpenoid saponins are the active components of the molluscicidal plants Tetrapleura tetraclea, Swartzia madagascarensis and Phytolacca dodecandra (endod). Figure 2 shows the molluscicidal saponin lemmatoxin from endod. The content of saponins in plant berries can reach up to 30% and some individual saponins are active at concentrations as low as 1.5 mg l$^{-1}$ (Ref. 22).

Field trials have been carried out on endod berries in Ethiopia. A pilot study over five years showed that overall prevalence of schistosomiasis in the population of the study area of Adwa (population 17000) dropped from 63.5% to 33%. Unlike most plant molluscicides, endod has been the subject of a number of toxicological investigations. More investigations would be required, however, to obtain widespread approval for general use (indeed, it is probable that no country has yet established regulatory criteria for the registration of plant molluscicides for public health use, nor has registration of any plant molluscicide been attempted in any country). A toxicological report on a standardized endod extract has been published which showed that, in oral, dermal and inhalation tests, the extract was either slightly toxic or non-toxic. The extract did prove to be a severe eye irritant. The main drawback to using endod in the field is that it is not effective in killing snail egg masses. However, it could still be of use as a cheap alternative in areas where synthetic molluscicides cannot be afforded.
Focus

Alpinumisoflavone

Fig. 3. Representation of some molluscicidal isoflavonoids, potential new lead compounds.

Compounds, and studies on their individual activities and toxicities are an obvious priority.

The case for combined use of synthetic and plant molluscicides

It is obvious that, for many years to come, the demonstrable effectiveness of niclosamide will ensure its central role in schistosomiasis control. Even its potential new lead compounds.

Given these circumstances, the most obvious role for plant molluscicides in the short and medium term is as a local, cheap supplement to niclosamide, to be applied using the simplest possible technology. In the longer term, the identification of molluscicidal molecules from plant sources may characterize a new lead compound for synthetic development that would match or exceed niclosamide’s target toxicity, be cheaper to produce, and have reduced non-target toxicity.

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Limburger Cheese as an Attractant for the Malaria Mosquito Anopheles gambiae s.s.

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In the process of bloodfeeding, female Anopheles can transmit malaria parasites to humans. At night, while searching for blood, these insects respond to visual, physical and chemical properties of humans. Current research concentrates on the identification of kairomones, which guide mosquitoes to humans. Earlier observations on the biting behaviour of Anopheles gambiae s.s. on humans have now resulted in the discovery of a remarkable attractant for this important malaria vector, and it is thought that this will accelerate the development of odour-baited traps for malaria mosquito surveillance and control in sub-Saharan Africa, as discussed here by Bart Knols and Ruurd De Jong.

The malaria situation in much of Africa south of the Sahara is rapidly deteriorating, mainly due to increased resistance of Plasmodium against chemoprophylactics and curative drugs. The development of effective control measures for Anopheles vectors, therefore, becomes increasingly important; a major constraint is a lack of understanding of the biology of Anopheles, including their host-seeking behaviour. In the same way as detailed study of tsetse behaviour assisted the development of effective trap/bait systems for their surveillance and control, more insight in the behaviour of mosquitoes will certainly assist in further knowledge on malaria epidemiology and the dynamics of vector populations.

In contrast with the extensive knowledge on the host-seeking behaviour of tsetse, remarkably little research has been done on mosquitoes, especially the nocturnally active Anopheles. Many investigations have underlined the influence of body heat, moisture and, to a lesser extent, carbon dioxide on mosquito host-seeking behaviour in the vicinity of the host. These factors seem so dominant that odours are believed to be involved only at distances where heat and moisture are no longer detectable. Carbon dioxide, a major constituent of exhaled breath, has been identified as an attractant for many mosquito species. It is generally accepted that oligophagous mosquito species use host-specific olfactory cues during host-seeking, but evidence for this is scarce. In fact, only one report exists where mosquitoes were attracted to odour independently of carbon dioxide, ie. Aedes aegypti L. to as-yet-unidentified human skin compounds.

Biting behaviour of Anopheles gambiae

Anopheles gambiae s.s. Giles, the most important malaria vector of the Afro-tropical region, is known to be highly anthropophilic and is attracted to carbon dioxide at a dose equivalent to that emitted by human (ie. ~300 ml min⁻¹ in a wind-tunnel setup). Field studies have indicated a preference for adults over children, and, although it was found that mosquitoes do not discriminate between sexes, it seems that certain individuals are more attractive than others. This preference indicates that, besides carbon dioxide, additional kairomones (that are not equally produced by individuals) influence host selection. It has been observed that, in still air, biting occurs preferentially on feet and ankles of a naked motionless human host. This preference correlates with particular combinations of skin temperature and eccrine sweat-gland densities. However, subsequent modification of the host's odour profile by washing the feet and ankles with a non-perfumed medical soap containing Unicura®, a bactericidal agent [2,4,4'-trichloro-2'-hydroxydiphenyl ether (1%)], resulted in a significant change of this preference. The fact that An. gambiae could be diverted from biting the feet and ankles to other body regions suggests that odours normally emanating from feet and ankles play a role in the selection of biting sites by this species. Furthermore, it is assumed that these odours are specific to humans and thus provide a reliable source for anthropophilic mosquitoes for finding their hosts. In other experiments, it has been shown that the biting behaviour of more catholic feeders is strongly influenced by exhaled breath of humans, of which the carbon dioxide content is a reliable odour source for opportunistic feeders.

Foot odour and Limburger cheese

The typical and distinct odour of human feet is caused by particular combinations of resident skin microflora and their environment. It has frequently been described as ‘cheesy’ and also the Dutch word ‘tenenkaas’ (literally ‘toes-cheese’) refers to its strong

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