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Short Communication

Thalidomide Revisited: Advances in Medical Research on Chiral Pharmaceutical Intermediates

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The rate of metabolism as well as the metabolic profiles of the enantiomers and the racemate of 2-(2,6-dioxopiperidine-3-yl)-phthalimidine (EM12), a teratogenic thalidomide analogue, were investigated *in vitro* and in the marmoset monkey *in vivo* and published in 1989, by 3 researchers (Hans-Josefi Schmahl, Wolfgang Heger and Heinz Nau) from Institut für Toxikologie und Embryopharmakologie, Freie Universität, Berlin, German.

The half-life of racemic EM12 and of the two enantiomers *in vitro* (phosphate buffer pH 7.40, 37°C) were all in the same range (12h). Two major hydrolysis products were found which were formed via amide cleavage of the piperidinedione ring of the molecule (EM 27 and EM 356). Their concentrations were similar. In contrast, EM 356 was the main metabolite of EM 12 present in the urine of marmoset monkeys following single i.p. or p.o. doses of 5 mg/kg body weight. About twice as much EM 356 was produced after administration of R-EM 12 than after administration of S-EM 12.

The concentration ratio of the metabolites obtained after p.o. and i.p. administration of the substances were in the same range. Separation of the EM 12 enantiomers present in urine suggested that considerable racemisation took place *in vivo*, although at a slower rate than *in vitro*: about 25% of the respective optical antipodes were present 5h after administration of the R-enantiomer and 7.5h after administration of the S-enantiomer (compared to 1.5h *in vitro*).

Results indicated that racemic EM 12 as well as its enantiomers are chemically and metabolically more stable than thalidomide; however, extensive racemisation occurs both *in vivo* and *in vitro*.

The metabolism and renal excretion of the enantiomers of EM 12 in the marmoset monkey (i.e. mammalian species) were shown to be stereoselective.

Use of chiral molecules in clinical practice may cause problems because different chiral forms of a drug (enantiomers) may have different biological activities--yet clinicians have little awareness of these risks. After discussion of the chemical conventions used to describe chirality, examples of the influence of chirality on the efficacy and toxicity of antirheumatic drugs were given.

It was recommended that single enantiomers should be used in biological experiments and clinical trials [1].

Chirality is a key factor in the efficacy of many drugs; thus, the production of single enantiomers of drug intermediates has become increasingly important in the pharmaceutical industry. Chiral intermediates and fine chemicals are in high demand from the pharmaceutical and agrochemical industries for the preparation of bulk drug substances and agricultural products.

There has been an increasing awareness of the enormous potential of microorganisms and enzymes for the transformation of synthetic chemicals with high chemo-, regio- and enantioselectivity. Biocatalytic processes for the synthesis of chiral pharmaceutical intermediates were reported by Patel RN [2].

The importance and practicality of asymmetric synthesis to obtain enantiomerically pure drug substances has been fully recognized by process chemists of the pharmaceutical industry.

Catalytic enantioselective processes would be particularly advantageous, compared to processes requiring stoichiometric amounts of chiral initiators, and would also be of interest from an environmental perspective. Since the commercialization of the Monsanto process for the manufacturing of L-DOPA in the early 1970s, catalytic asymmetric reactions have often been utilized in the commercial production of active pharmaceutical ingredients. Thus, focus on recent advances in the development of scalable enantioselective processes for chiral pharmaceutical intermediates, accordingly the paper by Iida T, Mase T [3] will be recognized.

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An effective and instructive example of a drug that has a different effect depending on the chirality of its metabolites is provided by thalidomide.

The thalidomide molecule contains an asymmetric carbon atom, but the form of the drug which has been used therapeutically and which has produced congenital malformations in man is the optically inactive form, that is (±)-thalidomide. The optical antipodes of thalidomide were synthesized in and Dr A. M. Creighton had supplied samples of both (+)- and (-)-thalidomide. The (+)-isomer, melting point 240° - 241°C, showed [α]D20+60° (c = 2 in dimethylformamide) and the (-)-isomer, melting point 241° - 242°C; showed [α]D20-58° (c = 2 in dimethylformamide). (±)-Thalidomide has a melting point of 271°C and, of course, is optically inactive. With these samples, was determined the acute oral toxicities of the three forms in mice, their teratogenic activity in the New Zealand white rabbit and their effect on the hypnosis induced by hexobarbitone in mice [4].

Thalidomide is a drug that was sold in the 1950s and 1960s as a sedative, anti-nausea, and hypnotic. It was a drug that had an extremely favorable risk/benefit balance compared to the other medicines available at the time for the same purpose (barbiturates). Today, however, it is used as a chemotherapy agent for various diseases.

Produced in raceme form, it was withdrawn from the market at the end of 1961, after being distributed in fifty countries under forty different trade names, including Contergan and Distaval. The withdrawal was due to the discovery of the teratogenicity of one of its enantiomers: women treated with thalidomide gave birth to babies with severe congenital alterations in the development of the limbs, i.e. amelia (absence of limbs) or varying degrees of phocomelia (reduction of the long bones of the limbs), generally more in the upper limbs than in the lower limbs, more often bilaterally, although with different degrees.

In 1961 McBride and Lenz made public the first cases of fetal abnormalities linked to thalidomide, including the forgotten data of 1957; In all, 1,500 cases were reported from 1957 to 1961. Also in 1961, McBride tested the drug on pregnant laboratory animals and confirmed its teratogenic effects.

In the U.S. market, on the other hand, thalidomide was never allowed to enter. Its entry was prevented by Frances Kelsey, an auditor at the FDA.

Thalidomide was withdrawn in different countries gradually from December 1961, first in Great Britain (on 2), than in Italy where the retreat took place in September 1962.

In 1962 Somers repeated the 1960 experiment, this time on pregnant animals with a more bioavailable form, and obtained positive results. The journal *Lancet* published an article showing that the how the administration of thalidomide to pregnant mice resulted in the birth of broods with severe limb malformations. Over the next few years, experimental evidence of the drug's teratogenicity accumulated in different mammalians (i.e. mice rabbit, chicken, rat, cats, guinea pigs).

In 1962, it was made compulsory to test the new drugs on pregnant animals to test their effects on foetuses. Thus, in September 2012, the drug company issued an official apology at the inauguration of a memorial to the victims in Germany (Stolberg).

Since 5 October 2009, the Italian State has paid a monthly allowance to thalidomide victims born between 1959 and 1965. On 20 August 2016, the Italian parliament approved a law structured as an extension of the previous one from 2009, setting a maximum limit of ten years to claim compensation. On 17 October in 2017, albeit seven months later than expected (February 2017), the Minister of Health Beatrice Lorenzin signed the decree to release compensation, giving the possibility to apply also to victims born in 1958 and 1966, as well as all subjects with malformations compatible with thalidomide syndrome.

50 years after the tragedy, producers apologized, but for patients it was not enough - Quotidiano Sanità 4 September.

Distributed between the 50s and 60s, the medicine against morning sickness had caused the birth of more than 10 thousand children with serious malformations, heart abnormalities and brain problems.

Teratogenicity is associated with only one of the enantiomers. It acts as an inhibitor of angiogenesis, i.e. the normal development of blood vessels, interfering with the development of the embryo, especially if taken during the first seven weeks of pregnancy. The hypothesis of using only the enantiomer that does not give teratogenicity in therapy has proved to be impracticable due to the spontaneous conversion between the two enantiomers that occurs in the body.

The human species was found to be sensitive to the dose of 1 mg/kg.

The molecule inhibits protein kinase alpha (IKKα) of protein IκB, an endogenous inhibitor of the transcription factor NF-κB. This factor is actively involved in the proliferation of cancer cells and the synthesis of many cytokines, such as interleukin-1, interleukin-6 and tumor necrosis factor (TNF-α). IL-6 and TNFα are responsible for febrile, painful, and osteolytic symptoms in patients.

The angiogenesis-inhibiting effect and the selective inhibitory power of TNFα synthesis of the drug have rekindled clinical interest in the use of thalidomide in many diseases, ranging from AIDS to certain types of cancer and Crohn's disease.

Since 1998, the medicine has been successfully used in the fight against multiple myeloma, a cancer of plasma cells, and in the last three years improved derivatives of the molecule, known as lenalidomide and pomalidomide, have also been approved, which are used with the addition of corticosteroids.

Thalidomide has also been approved for use in the treatment of Behcet's disease.

Thalidomide can also be used as a second-line treatment in the following human conditions: cutaneous manifestations of systemic lupus erythematosus, erythema nodosum and pain associated with leprosy. Sarcoidosis with early onset.

Targeted studies will be needed in the future in order to avoid such human tragedies and a huge waste of public resources so how would it be more useful to allocate them to more appropriate medical/health purposes.

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