

CHAPTER SEVEN

7.0 CONCLUSION

Despite the long history of the use of HpD as a therapeutic agent, the mechanism of its uptake and retention in tumour and normal cells remain ambiguous. The concept of selectivity of the oligomeric material in the tumour relative to its surrounding healthy tissue was undoubtedly regarded as important for the successful application of PDT. As a result of this, treatment of malignancies was always performed at a delayed time of 24-48 hrs post-injection of drug.

In the development of the alternative protocol of Immediate PDT as proposed by this centre, it was shown that at one-sixth the drug dose of HpD, better tumour response was obtained with Immediate PDT compared to delayed PDT. This finding suggests that the poorer tumour response obtained for delayed PDT may be due to the much reduced serum levels, which would have been fallen considerably from its peak by 24-48 hrs. With the perception of Immediate PDT, the notion of tumour localization and retention are no longer key features in the choice of a photosensitizer. One could use a photosensitizer that has a fast excretion rate from the body system but is equally effective for PDT and has negligible skin photosensitivity. For this purpose, the parent compound of HpD, Hp, a monomeric component was re-examined.

The confusion of the nature of Hematoporphyrin began at the onset of the study of photodynamic therapy which dated back about 90 years ago. The preparations of Hp which contained a small amount of the oligomeric material was thought to be responsible for the tumouricidal effect. Due to this, Hp was neglected as a possible photosensitizer for PDT.

However, it is apparent now that the timing of red light irradiation post injection is crucial with the development of the new protocol referred to as Immediate PDT which has enabled Hp to be introduced as a possible photosensitizer.

Investigations on the pharmacokinetics and the response of tumour with the application of Hp-PDT as compared to HpD-PDT were carried out. The results indicate that Hp has a rapid excretion rate via the liver, which is about 90 times faster when compared to the oligomeric component. Besides that, it exhibited a similar tumour response as HpD with an application of 3.5 times higher drug-light dose product. From the skin photosensitivity study, results show that Hp-PDT exhibited a very minimal skin photosensitivity as compared to HpD-PDT despite the fact that a higher drug-light dose product of Hp was required for tumour response. This study suggests that the drug-light dose product of Hp could be scaled up to a factor of 10 times or more for effective PDT and yet skin photosensitivity would still be manageable.

The results of the pharmacokinetics shows that the mean concentration of Hp in the serum decreased by a factor of about 1.6 times more when compared to HpD in the first 5-25 mins post injection during light irradiation. The PDT response revealed that there is still a factor of 2.2 difference between the drug-light dose product on top of the 1.6 factor from the difference in the serum level of drugs. This is possibly due to the higher phototoxicity of HpD over that of Hp. The other plausibility could be that HpD could have higher affinity for the endothelial cells in capillary vessels.

The pharmacokinetics and the tumour response studies have revealed primarily that the treatment effects are dependent on the exact time of treatment after the drug administration. Therefore, it may be useful to photoirradiate the tumour while injecting the drug simultaneously rather than to wait 5 mins after the injection before administering the light. This may help to potentiate maximal tumouricidal effects, during which period

the Hp and HpD level in the serum is sufficiently high. This implied that Hp will have longer time for vascular sensitization, while less amount of HpD is required to potentiate good tumour responses thereby also reducing skin photosensitivity. In order to investigate this further, investigation of Immediate PDT for different ways of drug administration could be employed. Instead of intravenous or intraarterial administration of Hp, a bolus injection of half the threshold dosage could be carried out followed by a slow infusion to maintain the concentration of Hp in the serum level. Hence, lower doses of Hp could still enhance the vascular impairment of the tumour. Moreover, Hp is rapidly excreted from the body system, thereby reducing prolonged cutaneous photosensitivity.

It is also useful to investigate a photosensitizer which has a moderate excretion rate in between Hp and HpD to allow for slightly longer retention period of the drug in the vascular space for light irradiation.

The development of the multicompartmental and multicomponent model seemed suitable in the extraction of quantitative pharmacokinetics parameters. Separation of the two components of the drugs and using different compartments for different tissues have apparently overcome the problems of the pharmacokinetics analysis. A quantitative understanding of the distribution and elimination of both the drugs were obtained. It may be desirable to investigate further the modelling of the multicompartment and two component model to validate the approximate model adopted in this study.

Studies using the simple red light source to photoactivate HpD in tumours using the conventional delayed treatment protocol showed that the halogen light source which is simple, reliable and cost effective is a suitable alternative to the laser for surface irradiation of a wide range of superficial malignancies for routine clinical application. The patients from the clinical trials had benefited from the treatment with the light sources with effective palliation control. The clinical trials using HpD and the conventional delayed treatment

would hope to substantiate the foundation for the future Hp-Immediate PDT programme at this local centre.

In conclusion, the study has established the basic techniques and procedures for viable Hp and HpD-PDT programme at this centre. The study has opened up new avenues of investigation. Further work will have to be initiated to further elucidate the findings of this thesis. These studies may contribute significantly towards the future direction of PDT research. It could make PDT a simple and a convenient modality for the treatment of cancer.