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NEWS

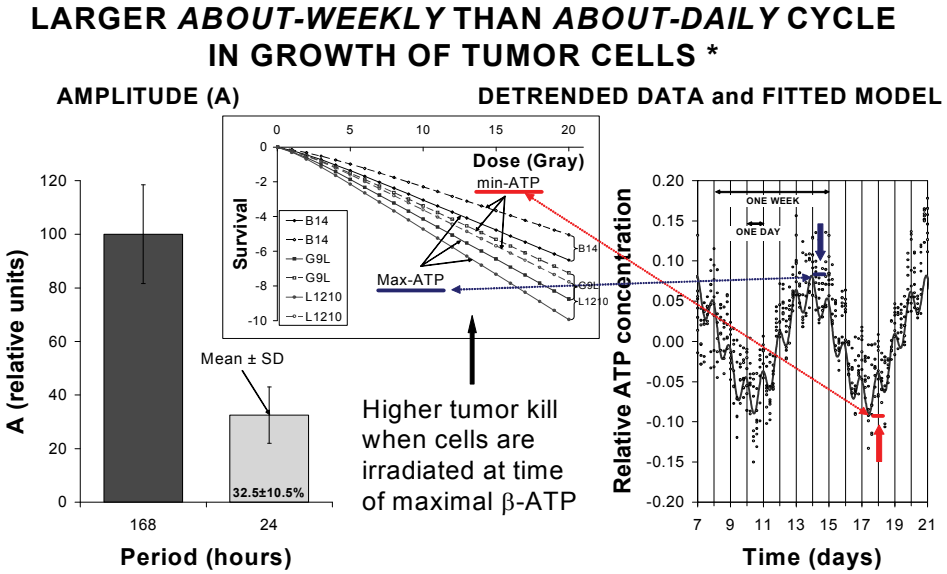
Chronopharmaceutics

A new Wiley book, edited by Bi-Botti C. Youan, so titled has the challenging subtitle "Science and technology for biological rhythm-guided therapy and prevention of diseases", which recognizes the fact, ignored by those developing pharmaceuticals, that one can also seek specific times when certain chemical structures best achieve their desired effects with least undesired consequences. This possibility of avoiding the lethality of a stimulus became obvious by 1955 when, in the same inbred strain, a stimulus given in the laboratory at one roughly predictable time led to convulsions, often with death, while given at another predictable time it was harmless.

Soon thereafter, this finding was extended to alcohol and to many drugs, Table 11.4, pp. 312–313. That with a fixed dose of ouabain, 75% of comparable rodents died at one circadian time while 75% survived, was surpassed with all dying at one time or all surviving, a few predictable hours earlier or later, from the same dose of an adrenal cortical inhibitor Su-4885, Figure 11.1, p. 260. In the case of the experimental animal laboratory, the gains were great, in dealing with blood pressure and cancer, and, by 1978, cancer chronotherapy doubled the two-year disease-free survival, when tumor temperature was used as a marker rhythm for chronotherapy, Figure 10.6, p. 228.

On October 2, 1968, Alejandro Zaffaroni anticipated, as he put it in writing, "a most enjoyable and friendly relationship on a personal and scientific basis to attempt to incorporate findings in chronobiology to the design of advanced therapeutic regimes". From the entity he created, ALZA, which bears the first two letters of his first name and surname, the book on Chronopharmaceutics contains a contribution by a team of three individuals, which reports a pulsatile delivery dosage form, a 2-hour (h) Chronset and a 6-hour Chronset. The reader will have to decide the extent to which Zaffaroni's vision was implemented over 41 years later.

Other papers in this book also aim at drug delivery at predetermined times, having primarily circadian



* Nonlinear spectral analysis of data pooled from four kinds of tumor cells, each cultured at a pH of 6.9 (experiment #1) and 7.3 (experiment #2). Data shown for weeks 2-3 (total 6 weeks, exhibiting persistent cycles of similar relative prominence).

Fig. 1

optimization in mind. The active controlled release microchip of Langer's group in Chapter 9 allows delivery of more than a single agent, as seen in Figure 9.4, p. 195. It also seems to have demonstrated efficacy against a 9L glioma rat tumor model. As illustrated in Figure 1, circaseptan optimization in this model may be even more important than circadian chronotherapy. The need for extending the focus beyond circadians and for reliance on marker rhythmometry is emphasized in the last two chapters. Therein, methods are also presented for N-of-1 studies with an inferential statistical basis. Timing drug delivery is more than a gimmick (Kennedy BJ: A lady and chronobiology. Chronobiologia 20:139–144, 1993). Many challenges remain. Triangulation is too complex and invasive when blood is used. Cancer markers in saliva should be tried for timing.

Paul Ehrlich looked for compounds with specific structures to treat specific diseases that would leave everything else alone. Likewise, we can keep on looking, if not for magic bullets, then for timing that is as essential as dosing. Administration of pharmaceuticals at the "wrong time" can kill with a dose that is most helpful when it is given at the "right time! "Right" and "wrong" times are best estimated on the basis of marker rhythms.

The book is recommended to all who deal with pharmaceutics, as well as with pharmacology. As noted by Bi-Botti C. Youan, the rhythms' milestones date back to the 7th century BCE. What the book teaches us today should be part and parcel of the education of all health care providers and recipients. It could stem enormous current waste by those who have not yet acquainted themselves with phase-zero trials. Therein, timing takes first rather than last priority, as is currently the case in industry. By systematically testing new drugs at different rhythm stages at the outset, one may not only avoid discarding a useful drug if tested at the wrong time, but one may also obtain an estimate of what optimal rhythm stages may be, and assess the extent of difference in response from administering the drug at the presumably best or worst times.

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