synthetic antidiarrheal drugs

synthesis — preclinical and clinical pharmacology

edited by WILLEM VAN BEVER
and
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FOREWORD

This monograph represents the individual research efforts by an unusually fine group of chemists, biologists, and clinicians with the goal of finding a better antidiarrheal agent. In 1956 this group discovered that the compound diphenoxylate possessed good antidiarrheal properties but, if taken orally, did not reveal its strong morphomimetic qualities. Since then, it has been used extensively and effectively over the world with no demonstrated cases of morphinelike dependence. Pursuing their research efforts further, these scientists determined the active principle of diphenoxylate to be difenoxin.

After extensive comparative clinical trials of diphenoxylate and difenoxin the latter has been shown to have five times the potency of the former. But difenoxin like diphenoxylate retains enough morphomimetic properties to be of some concern. Encouraged by their success with difenoxin, the group undertook the formidable task of finding a substance whose antidiarrheal properties were separated from its morphomimetic properties. This five-year search involved the synthesis of several thousand compounds.

The tenacity of purpose of the group is indicated by the fact that little success has attended previous efforts to separate analgesia from its dependence-producing properties with morphinelike drugs.

Lack of success in such efforts would serve to deter a less dedicated group from pursuing a long course of investigations of this type. It is all the more remarkable that success was achieved.

Best of all, it produced a most effective compound, loperamide. In loperamide they have produced a substance with such low morphomimetic properties that it has been shown to have no significance whatsoever either in laboratory or clinical studies. Loperamide has now had extensive clinical trial under controlled conditions and has been found to be a most highly

effective agent during long-term, chronic use in otherwise intractable diarrhea. The project represents a fine example of what can be accomplished by concerted and unremitting effort.

The author is unaware of any other publication which deals so comprehensively with the problem of diarrhea. This contribution can be recommended highly not only for its scientific and clinical worthiness but as a classical example of what can be accomplished in solving a problem which has hitherto found little attention and been relatively of little interest to most investigators.

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PREFACE

Diarrhea is a widespread condition that is often reported to the physicians for treatment, in addition to countless instances where diarrhea is treated by folklore medicine.

Nearly all practitioners of general medicine and often other medical specialities prescribe antidiarrheal drugs to their patients. Moreover, numerous inquiries on the treatment of diarrhea are daily referred by the patients directly to pharmacists, nurses, and other health professionals. The extent to which antidiarrheals are used is evident from the fact that of diphenoxylate, the only specific antidiarrheal available until recently, more than two billion doses have been prescribed in the last six years. Besides, there is widespread use of other nonspecific medications for diarrhea that are prescribed by physicians and can also be purchased directly from pharmacists.

In spite of such widespread use of antidiarrheals, readily available information for use to physicians and other health professionals is surprisingly scanty. Textbooks of pharmacology as well as those of medicine either do not mention them or refer to them only in passing. Because of this total lack of information on the various aspects of antidiarrheal action and their uses in medicine, we undertook to assemble a complete monograph on modern antidiarrheal drugs. We hope that our efforts will fulfill a long-standing need of the profession.

We limited the scope of this monograph to the extensive discussion of only those antidiarrheals which are specific for diarrhea and are used as such in modern human medicine. Many other pharmacological agents which reduce diarrhea only incidental to their other actions, or those drugs which are used in veterinary practice are not included here.

A glance over the contents of this book will easily reveal that the subject of antidiarrheal drugs has been discussed rather extensively by those who have been themselves involved in one or the other aspect of development, research, or clinical applications of those drugs. Only these contributors could impart a personal touch to the narration of many aspects of scientific endeavors which go into the making of an antidiarrheal drug.

The arrangement of presentation evolved to provide a scientific basis for rational therapy of diarrhea. Along with the data, critical description of methodology is given in order to bring about full appreciation of what goes into the making of a successful antidiarrheal drug. Although the research aspects are not fully elaborated, sufficient description of research methodology and current problems is included so that future research in various aspects of antidiarrheal drugs is facilitated.

We believe that this book will be useful to clinicians, pharmacologists in industry as well as in academia, advanced students in pharmaceutical and medical sciences, teachers in medical schools, and above all, to practicing physicians and drug-consultant pharmacists. We shall consider ourselves highly compensated for our efforts if the book can accomplish the above objectives.

Willem Van Bever

Harbans Lal

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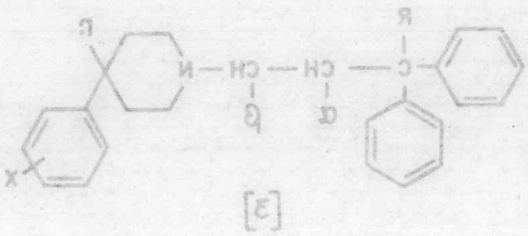
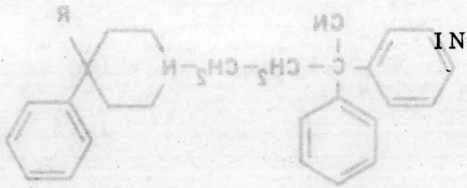


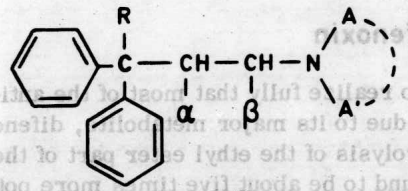
CHAPTER I



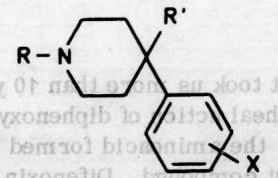
INTRODUCTION

Paul Janssen

In 1956, the first synthetic antidiarrheal drug, diphenoxylate, R 1132 [4a], was discovered in our laboratory in the course of an experimental long-range program designed to explore systematically the relationship between the chemical structure of 3,3-diphenylpropylamines [1], related to methadone, and 4-phenylpiperidines [2], related to pethidine, and the pharmacological activity of these compounds.



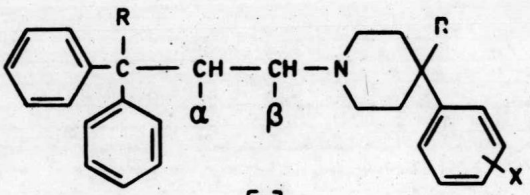
[1]



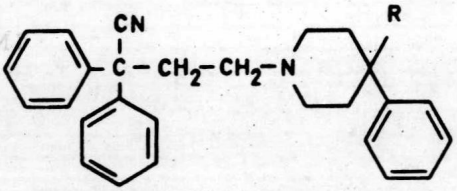
[2]

Diphenoxylate, the prototype of a series of hybrid molecules [3], chemically related to (1) and (2), was found to be an extremely potent constipating and antidiarrheal agent in laboratory animals as well as in man and to be relatively free of effects on the central nervous system (CNS) of the morphine-like type. The drug was brought on the market in 1960 and has been extensively used for the symptomatic treatment of diarrhea ever since, i.e., an estimated 3,200,000,000 tablets of 2.5 mg (Reasec, Lomotil, Diarsed, etc.) were sold in the 15-year period from 1960 to 1974.

The efficacy of the drug is undisputed and its safety margin excellent, particularly in adults. Tolerance is not a problem in chronically treated patients and the abuse liability of the drug is negligible; no serious cases of drug abuse have been reported up to the present day.



[3]



[4a] R = $COOC_2H_5$

diphenoxylate

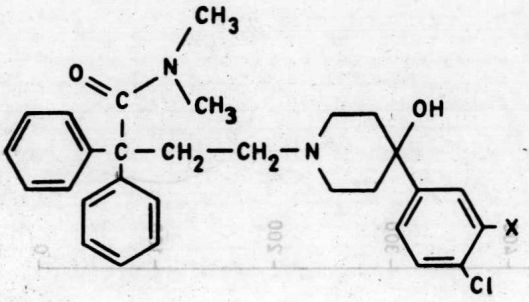
[4b] R = COOH

difenoxin

It took us more than 10 years to realize fully that most of the antidiarrheal action of diphenoxylate is due to its major metabolite, difenoxin [4b], the aminoacid formed by hydrolysis of the ethyl ester part of the parent compound. Difenoxin was found to be about five times more potent than diphenoxylate (0.5 mg difenoxin tablets being at least as effective as 2.5 mg diphenoxylate tablets) and to have an even weaker effect on the CNS.

Between 1956 and 1968 several thousands of new derivatives of structures [1], [2], and [3] were prepared and pharmacologically investigated. Many of these compounds turned out to possess interesting morphinomimetic, anticholinergic, or neuroleptic properties, but all efforts to find specific antidiarrheals superior to diphenoxylate failed, the active molecules being either less potent, shorter-acting, or less specific, i.e., more active on the CNS. Superior compounds are indeed hard to discover in this field.

In 1969, when a new method for the synthesis of basic amides of type [5] was found, interest in the field of antidiarrheal drugs was revived. It was found that several members of the new series, but in particular loperamide [5a], chemically related to the classical neuroleptic haloperidol [6], and fluperamide [5b], chemically related to the long acting neuroleptic pentfluridol [7], were not only more potent and longer acting than diphenoxylate in animals and in man, but surprisingly free of morphine-like or

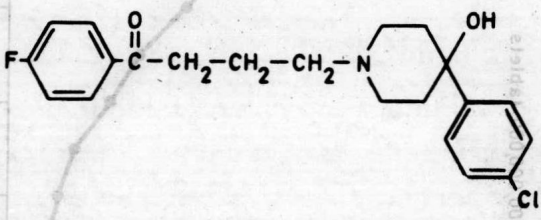


[5a] X = H

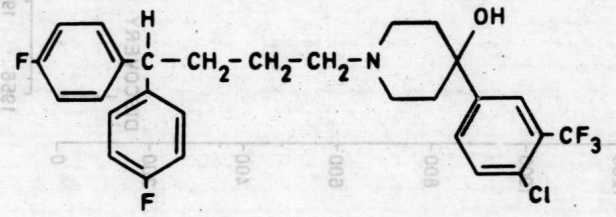
loperamide

[5b] X = CF_3

fluperamide



[6] haloperidol



[7] penfluridol

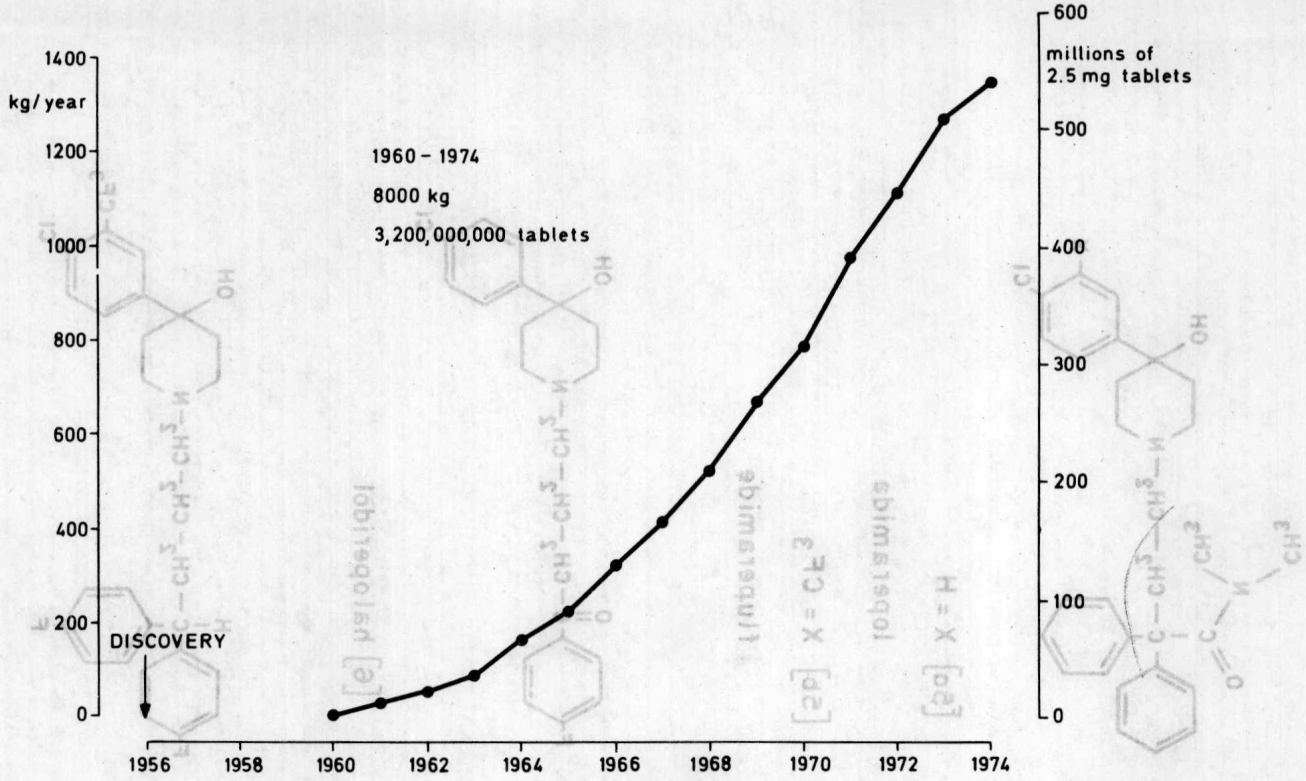


Fig. 1. Worldwide use of diphenoxylate in clinical practice.