Good Clinical Practice In Clinical Drug Trials – What You Need To Know

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Research is a systematic investigation designed to produce generalizable knowledge. The results are usually applied to other populations, published and disseminated. Clinical research is vital to finding cures and providing a better quality of life overall.

Although experimental medicine and Biomedical Research like several other research activities carry a degree of hazards, they have benefits that outweigh these hazards when conducted within the framework of respect for autonomy, justice and human rights. This is what GOOD CLINICAL PRACTICE (GCP), an international ethical and scientific quality standard for designing, conducting, recording and reporting research that involves human participants, is all about.

Its doctrines are based on current guidelines of practice in clinical trials adopted by the European Union, Japan, the United States, Australia, Canada, the Nordic Countries and WHO and finally approved by these countries in 1996 at the International Conference on Harmonization (ICH).

Why set standards?

Guidelines and Standards are developed for various reasons. In clinical research, standards are set to facilitate data integrity and accuracy while ensuring participant safety and well being. The standards set promote high quality research whose outcomes are internationally acceptable when accredited international guidelines are adhered to.

The objective of GCP is to provide a unified standard to facilitate acceptance of study data by regulatory authorities worldwide.

Compliance with GCP ensures that the rights and safety of research participants are protected, in accordance to the Declaration of Helsinki.

So grave is the issue that the European Union in 2004 promulgated the Directive on GCP into law to ensure that GCP is applied to all international clinical trials.

The entire 59 and 104 paged ICH and WHO guidelines can be summarized into 4 points thus:

- Forming research ethics committees
- Procedures of informed consent
- Standards of care
- Distributive justice (such as post-trial benefits or compensation for injuries arising from research)

Other standards and guidelines are:

- The Nuremberg Code
- The Belmont Report
- The Council for International Organization of Medical Sciences – CIOMS

These guidelines are instructions, given by an official or organization describing how to carry a particular task out especially when the task is a difficult one. Guidelines differ from REGULATIONS which are official rules made by Government or some other authorities to control individuals and activities, in order to ensure that tasks get carried out according to set patterns.

While regulations are rigid, with an element of control, GUIDELINES help individuals make decisions or form opinions that will aid accomplishment of the task.

This mini-workshop has been organized to intimate our community with GCP guidelines for reasons, some of which have been enumerated below:

There is very wide array of Research opportunities in Nigeria, particularly, in Lagos with the wide array of pharmaceutical companies who have need for clinical trials on their new drugs. Newer diseases are being discovered daily, prevention and cures for which need to be ascertained; technologic advancement continues unabated.

On the global scene, until about 10 years ago, 90% of over 50 billion USD annually devoted by pharmaceutical companies to clinical drug trials was utilized in North America and Europe where these researches go on. Little or nothing came to the developing countries in Africa.

With the influence of such organizations like United Nations and WHO and the emergence of Public Private Partnerships however, more drugs are now being targeted at diseases of these less developed countries.

The significance of this is that, dynamics changing in favour of the developing countries with instances of clinical drug trials increasing dramatically in Africa especially in South Africa. South Africa is prominent in this activity because of the much earlier foresight of capacity building in this wise over sixty years ago.

The rest of Africa is yet to show significant activities in clinical drug trials.
This can be our opportunity as the Public Private Partnerships have the thrust to sponsor research and development of drugs for these so called "Neglected diseases of the Poorer Nations". Nigeria therefore has to be ready. She should participate in the clinical trials of drugs that will eventually be used by her citizens, to avoid being sidelined.

Though the benefits of these international interactions and collaborations are enormous; the sanctions for defaults are even more gruesome, the need to be left out in this race. It must realize that it can no longer with her excellent pool of brilliant researchers should not be left out in this race. It must realize that it can no longer be content to believe in a big world but rather, a world that has become a tiny global village where a lot of interactive academic activities are going on. There is therefore need for capacity building. Researchers must be willing to avail themselves of the necessary training on Research Ethics; be willing to change from the old to the new. These efforts will be personal as the evidence of desire is, pursuit.

Recently an association was birthed in Nigeria- the Association for Good Clinical Practice in Nigeria (AGCPN), an initiative which originated from the University of Nigeria, Teaching Hospital, Enugu under the leadership of Dr. Ifeoma Okoye.

In Ibadan, University College Hospital/ University of Ibadan Medical School, there is also an existence of the Prof. Clement Adebamowo’s West African Bioethics Initiative under the auspices of the National Institute of Health, USA.

CMUL is more than able to rise to similar tasks, set up a system that will ensure conduction of research in such a way that human research subjects are protected, unethical, averse and unnecessary treatments are prevented.

In the not too far future, CMUL researchers will have more opportunities for international collaboration in research, hence the need for capacity building.

What are the requirements?
A very strong Institutional Review Board, IRB. Knowledge of GCP Guidelines hence, training, training & more training.
Research Investigator
IRB’s roles
Ethics
Approve protocol, consent form, the information to be given to trial subjects, recruitment methods (e.g. poster, advertisement, internet)

Who can be an Investigator? According to GCP Guidelines, an Investigator:

- must have necessary training, qualifications and appropriate experience in clinical drug trial;
- must have up-to-date CV which will describe the Investigator’s education, training and experience that qualifies him/her as an expert in clinical investigation of drugs. CV must state current appointment and knowledge in GCP;
- must ensure study is justified;
- must be able to select trial site that is in accordance with GCP Guidelines;
- must be able to make available time and be prepared to be available for regular meetings;
- knowing and following study protocol;
- selecting, knowing and training suitable study personnel;
- identifying and screening suitable subjects;
- obtaining informed consent from trial subjects;
- interacting with trial subjects as clinic appointment times will be much longer than usual;
- ensuring protection of trial subjects;
- briefing research team members and reviewing progress of the trial;
- ensuring the quality of laboratory evaluations;
- generating and keeping all source data;
- maximizing data quality;
- ensuring timely and efficient safety reporting;
- maintaining good trial files and archives;
- completing paper work with meticulous documentation;
- attending to auditors and inspectors - in case of sponsored projects;
- disclosing all financial conflicts of interests.

One of the roles of the Investigator is the development of an acceptable CONSENT FORM which must fulfill all requirements from the local area, Sponsor and the national and international regulatory inspectors like NAFDAC (National Agency for Food and Drug Administration and Control) and FDA (Food and Drug Administration).

- Non-technical language should be used to avoid ambiguity.
- For non-English speaking participants, the statements in the Consent form must be translated and back-translated till it is ensured that both parties understand the terms in the Consent Form clearly.
- The consent must be read to the subject.
- Subject must read it too.
- If accepted, subject signs, witness signs and the attestations are dated.
- There should be no coercion of any form.
- The consent form should contain the following elements:
  - Statement that the study involves research;
  - Purpose of the research;
  - Duration of subject’s participation;
  - Description of procedures to be followed;
  - Identification of experimental procedures;
  - Reasonably foreseeable risks/discomforts;
  - Benefits to the research subject or others who may benefit;
  - Appropriate alternative treatments or procedures that may be advantageous;
  - Extent of confidentiality of records and that there may be inspections;
  - Compensation arrangements and source of further reimbursement;
  - Treatments for study related injury and contact/source for further information;
  - Contact for further information about the study and subject’s rights;
  - Statement that subject’s participation is voluntary;
  - Statement that subject’s refusal to participate involves no penalty or loss of benefits.

Conclusion: The above is only the tip of the iceberg. Further documentation below from other Presenters in the Team will throw more light on preparation for GCP. The other Presenters are.
will describe the journey of every new drug: 

**Dr. Osuntoki** - Benefits of collaboration in clinical research; 

**Dr. Wellington Oyibo** - Ethics: Composition and role of IRBs in clinical research; 

**Mrs. Hauwa Keri** - The role of NAFDAC in clinical drug trials; 

**Dr. Sade T. Ogunsola** - GCP in clinical Drug trial, a practical experience.

**REFERENCES:**


**The Journey of Every New Drug by Herbert Coker, PhD.**

In the context of Good Clinical Practice (GCP) the advent of new drugs is normally predicated or enshrined in the principles and procedures involved in orthodox clinical research.

Guidelines in GCP emphasize two main points viz: protection of subjects or patients and the science associated with validity of data and quality assurance of procedures involved in the clinical trials of new medicines, pharmaceuticals and biotechnology derived medications and medical appliances, and diagnostics.

An ideal modern drug is the successful candidate of the many thousands of evaluated candidates showing promise in a particular disease condition.

A promising compound or drug candidate must undergo extensive animal and human trials in consultation with NAFDAC (the National Agency for Food and Drugs Administration and Control), the sole Government Regulatory Agency on the Registration of Drugs, Pharmaceuticals, Diagnostics, Biologicals, Biotechnologicals etc. Drug Clinical trials and Good Clinical Practice under stringent ethical conditions must evince acceptable evidence of efficacy and safety to quality for registration as new medicines.

Drug discovery and development has attained a highly sophisticated systematic processes. There has been a quantum leap from the original activity guided natural product isolation and pharmacological evaluation to complex procedures involving molecular biology and genetic manipulation, vast molecular libraries and automated screening, and computer assisted drug design. Likely candidates are then subjected to animal studies preceding possible human clinical trials.

Pharmacological Research and Drug Development in Healthcare Delivery.

Medicines are medically recommended remedies intended for ameliorating disease conditions, and restoring good health and vitality to man. However drugs or pharmacologically active substances have to be developed into suitable forms for human use.

The final (or finished) product reaching the clinics and certified suitable and safe for medication purposes is usually the end-product of the combined efforts of numerous research scientists and professionals in the research and development (R & D) of new medicines or drugs.

The team of expert researchers, ideally, may consist of the following:

- the Pharmaceutical and Medicinal Chemist
- the Pharmacognost, the plant biologist, marine biologist, botanical chemist, biochemist and microbiologist
- the tissue pharmacologist
- the experimental and human physiologist
- the clinical pharmacologist and toxicologist
- the pharmaceutical technologist or drug formulation expert
- the clinical pharmacist, biopharmaceuticist and pharmacokineticist
- the pharmaceutical physician and drug clinical trials expert.

Drug registration and regulatory agencies e.g. NAFDAC.

Registered and certified drugs are dosage forms of medicines and these are pharmacotherapeutic agents that have been subjected to controlled Clinical Trials during drug development and are registered for use in Nigeria by NAFDAC.

Pharmacotherapy ensures that efficacious medication is predicated on well-defined clinical end points, such as fever clearance, pain abatement etc. Surrogate markers such as reduction in blood pressure or blood cholesterol which can be correlated with patients' response or clinical outcome can also serve as end points.

The ultimate goal of Pharmacotherapy is achieving definite therapeutic outcomes ensuring the patient's restoration to good health, better quality of life, vitality and contribution to the country's economic progress and development.

Quality Control and Drug Quality Assurance presupposes that drugs irrespective of formulation are released adequately for absorption.

Formulations in Drug development include solids (e.g. tablets, capsules, caplets) Liquids, inhalations, transdermal, injectables etc.

Bioavailability refers to the measurement of the rate and extent of drug delivery to systemic circulation (i.e. the
Good Clinical Practice in Clinical Drug Trials

blood and organs of the body). Biopharmaceutic studies allows for rational formulation of medicinal products.

For solid dosage forms – factors that may affect systemic bioavailability include:

- disintegration of the solid dosage form in the aqueous physiological fluid of the gastrointestinal tract, thereby releasing the active drug constituent of the tablet or capsule.
- dissolution of the drug substance released in the gastrointestinal fluid compartment, "solution" and subsequent absorption of the drug substance released in the gastrointestinal tract, thereby releasing the active drug constituent of the tablet or capsule.

Usually, medicines regulatory agencies such as NAFDAC are statutorily involved in the design of these trials.

Procedures Followed in Drug Design

The common traditional method employed by chemists in the search for new active medicinal compounds involves the initial consideration of a "Lead Compound" (usually of natural origin) known or observed to have a particular activity and attempting to modify or improve on its medicinal properties by structural variation based on chemical intuition and isosteric consideration, until a more highly active compound with minimal (undesired) side effects is produced. Many of the "Leads" have their antecedents or origins in folklore medicine, Traditional Medicine Practice or chance observation of some chemical entity.

Pharmaceutical companies are usually the champions of drug development although the early research, which leads to identification of either a biological target such as a new cell membrane receptor, or a new lead compound that interacts with a biological target, may also be initiated in academic institutions.

Techniques such as computer-assisted drug design are employed to elucidate the three-dimensional structure of a particular biological target and to design a molecule that interacts specifically with that receptor target. Drug researchers also have access to libraries containing large numbers of molecules which are screened against multiple in vitro biological targets using high-throughput computerized processes looking for a significant receptor-ligand reaction.

More recent advances in biotechnology have provided drug researchers with new biological targets such as cell membrane channels, various cell lines as well as active complex biological proteins. An example of this is the discovery of erythropoietin as a key regulator of red blood cell production. The identification of the gene encoding its amino acid sequence, and the subsequent insertion of this human gene into a non-human mammalian cell, allowed erythropoietin to be mass-produced for the treatment of anaemia in patients with renal failure. We are not too sure if this application will help in the treatment of Sickle Cell Disease (SCD).

Technological advances notwithstanding, serendipity has been responsible for many of today's medicine. Stickfast, for example, was initially investigated in clinical trials as a proposed anti-arrhythmic drug, but was noted to have a particular adverse effect. This led to a re-evaluation of its development plan, and its subsequent commercialization as an erectile dysfunction treatment.

Other examples include:

- The Opium Alkaloids (Opio) and Morphine, Codeine, Heroin – natural narcotic alkaloids from the plant Papaver somniferum – formed the template for the development of less - addictive and potent analogues such as Pentazocine, Meperidine, Levaphanol.
- Quinine, a naturally occurring antimarial drug from Cinchona bark served as template for the development of synthetic analogues such as chloroquine, amodiaquine and mefloquine (the quinolines).
- Another important antimarial of natural origin is the sesquiterpene Lactone, Artemisinin from Aretea annua (Quinghaosu). Derivatives of artemisinin include arteether, artesunate and arteether.
- Lignocaine and procaine, commonly used local anaesthetics have their antecedents in Cocaine, a natural alkaloid from the plant Erythroxylon coca.
- TUBOCURARIN is a naturally occurring curare plant alkaloid, (a neuromuscular blocker once employed in major surgery) was to be an object of extensive studies. Analogues with safer and more tolerable properties were later introduced in surgery. Professor J.B. Stanley (University of Strathclyde 1982) introduced a successful and potent biodegradable neuromuscular blocker for use in surgery – Atracurine Besylate. The drug was jointly developed by Stanley and Wellcome Pharmaceuticals. The first major drug to come out of an academic establishment.
- Anticancer agents (cytotoxic compounds) – such as Taxol, Vincristine, Vinblastine are plant derivatives.
- Willow bark is the source of Salicin. Salicylic Acid is a metabolite of Salicin. Acetyl Salicylic acid, Aspirin, is an acetyl derivative of Salicylic Acid. Aspirin – formed the template for the development of potent NSAIDS e.g. Diclofenac, Indomethacin, Flinamic, Profenid, Celebrex.
- Animal Organs or Parts such as the adrenal medulla of sheep is the source of adrenaline (epinephrine) a potent vasoconstrictor and haemostatic agent. Analogues of adrenaline include noradrenaline (isoprenaline), orciprenaline, solotanrol and sultanamol which have demonstrated different physiologic activities.
- The Pancreas and its islets of Langerhans is the source of insulin which plays a major role in diabetes disease.
- The fungal microorganism Penicillium notatum became the natural source of the Penicillins and Cephalosporin antibiotics.
- Products of Biotechnology such as the endocrine hormones e.g. Insulin, Oxytocin.
- Histamin from mast cells, cholinergic fibers of the gastric mucosa became the template for the development of potent H1-receptor blockers such as Cimetidine, Pantoprazole.

Once a promising new compound has been identified, it needs to undergo thorough testing to ensure that it works and is safe. Usually only a handful of the thousands of compounds tested make it through the clinics as new drugs.

Animal studies

Toxicology studies in animals are conducted before a compound can be used in humans, and government medicines regulatory agencies such as NAFDAC are statutorily involved in the design of these trials. Usually
two mammalian species are tested, such as rats and guinea pigs, using single and repeated dose administration regimens.

Clinical trials
The outcomes of the animal studies in terms of appropriate dosing, efficacy and safety are strong indications for possible human studies. Clinical trials must be conducted according to Good Clinical Practice, which defines a set of very strict conditions developed by international regulatory bodies in agreement with the principles espoused in the Declaration of Helsinki.

The design of these trials is determined in consultation with NAFDAC. There are four major phases of trials in the development of a new medicine.

Phase I
Phase I trials are typically conducted in healthy young male volunteers in groups of about 10-20. They are designed to assess how the drug is absorbed, distributed, metabolized and excreted by the body (that is, pharmacokinetics) and to establish the safe dose for phase II trials.

Phase II
Phase II trials are designed to examine what effect the drug has on the body (that is, pharmacodynamics) such as heart rate, blood pressure and cognitive effects, depending on the disease the drug is being developed to treat. These studies are usually conducted in 50-100 patients with the disease rather than healthy volunteers as in phase I.

In Phase I and II trials a very low dose of the investigational drug is usually given to a small number of people who are then monitored closely in a purpose-designed early phase unit. An early phase unit is similar to an intensive care ward with about 10 beds, each with sophisticated monitoring and emergency treatment facilities such as electrocardiograms, electroencephalograms, blood chemistry and haematology analysers, oxygen, intravenous fluids and resuscitation equipment. These units are often located within a hospital. If the first participants show no ill effects the dose is increased in the next group. This process is repeated several times until a minimum effective and maximum tolerated dose is established.

The maximum tolerated dose is reached when a specified percentage of participants experience adverse events as predefined in the study protocol.

Phase III
Phase III trials involve larger numbers of patients with a particular disease or condition and are usually randomized comparative double-blinded studies. The comparator is either placebo or an active drug already well established as treatment for the disease under investigation, or both. Typically, several hundred patients are exposed to the investigational drug in these trials, which are designed to show efficacy and safety and to better determine the appropriate dose range. The cost-effectiveness of a drug is sometimes assessed during the phase III trial stage. In a typical development program for a new medicine, several phase III trials are required by the regulatory authorities. Unfortunately, even with a large-scale phase III program, uncommon adverse events may not be detected until the new medicine is used widely in the community. As a rule of thumb, you need to expose about three times as many patients to a drug to reliably detect an adverse event that has a particular incidence; for example, to detect a 1 in 1000 event, 3000 patients need to be exposed.

Phase IV
Phase IV (post-registration) trials are those undertaken after the new medicine has been registered and are usually randomized controlled trials. They are designed to answer important questions which help determine its clinical position (for example first, second, or third-line use), cost-effectiveness, and safety profile in certain patient populations.

Phase IV trials may be very large studies involving thousands of patients for several years. They are very expensive but often, more useful than the earlier registration studies because they allow broader, more realistic patient groups to be studied. Pharmacovigilance is an integral part of the post Phase IV scheme.

Case Study in The Journey of every new Drug
Development of Cimetidine (Tagamet®), an Anti-Ulcer Drug (and Histamine H₂-receptor antagonists)
This is a classic and elegant testimony to the importance of multidisciplinary approach to research and drug development. Tagamet is the result of the combined efforts of the chemist, the experimental pharmacologist, and the human physiologist.

The Pepsin Ulcer Disease
Duodenal and gastric ulcers (peptic ulcers) affect between 10 and 20% of a population of people who are otherwise relatively fit. The disease causes pain and illness with appreciable discomfort, and often results in a measurable economic loss both to the patient and the nation.

Duodenal and gastric ulcers are localized erosions of the mucous membrane of the duodenum or stomach respectively which expose the underlying layers of the gut to the acid secretions of the stomach and the proteolytic enzyme pepsin. It is believed that the ulcerative erosion of the stomach and duodenal wall is caused by the effect of excessive acid in the stomach.

The traditional treatment had always been by the use of palliative acid neutralizing agents, antacids (e.g. Aluminium hydroxide and Magnesium trisilicate preparations) and anticholinergics, thereby reducing the irritating effect of the excess acid and also the effect of pepsin. This mode of medical intervention merely abated the discomforting experience of ulcer sufferers as only a low proportion of these lesions got completely healed.

Hydrochloric acid is physiologically essential for digestive purposes, but in excess it becomes injurious to the stomach wall.

Surgery has always been employed as an alternative to drug treatment. This involves the excision of the part of the stomach (e.g. partial gastrectomy) or selectively removing vagal nerve branches supplying the acid secretion region. The attendant hazards associated with such procedures are only known to gastroenterology surgeons.

It had been shown earlier, round about 1920, that histamine when injected into dog caused the secretion of gastric acid and that histamine exists naturally within the
lining of gastric mucosa. The relationship between these three chemical messengers, acetylcholine, gastrin and histamine was not too clear to physiologists for a long time.

The introduction of H₁ - histamine receptor blockers or antagonists such as Cimetidine (Tagamet*) and Ranitidine (Zantac*) was to produce a very marked change in the management of ulcer patients. The medical use of cimetidine and ranitidine brought about complete healing in almost 90% of patients suffering from peptic ulcers.

The Physiology of Ulcer

Figure 1: Diagram of the stomach showing vagus nerve and position of G cells (producing gastrin) and parietal cells (producing HCl).

Figure 2: Three chemical messengers stimulate the production of hydrochloric acid from the gastric parietal cell. The formulae show acetylcholine cation, histamine monocation (the most prevalent species at physiological pH of 7.4), and human gastrin 1.

Histamine Receptors

In 1910, Dale and Laidlaw working at the Wellcome Physiology Research Laboratories in London, published the first of a series of papers describing the pharmacological effects of histamine, and precisely the powerful effect of histamine in stimulating contractions of smooth muscle and its potency in lowering blood pressure. These observation's paralleled observed symptoms evinced during inflammatory processes, allergy and shock.

At that point in time it was generally assumed that histamine was a principal mediator of inflammation and shock, a suggestion which stimulated a search by Bovet in Paris for substances capable of neutralizing these apparent injurious effects of histamine. Bovet's findings led to the development of the classical antihistaminic drugs for the treatment of allergic conditions such as urticaria and hay fever (e.g. Mepyramine and Diphenhydramine).

However these drugs failed to antagonize other histamine induced actions such as stimulation of gastric acid secretion in the rat, cat or dog; stimulation of the isolated aorta of the guinea pig; inhibition of rat uterus contractions. It was also found that these antihistamines reduced the intensity of, but did not completely abolish, vasodilator actions of large doses of histamine, and in 1948 it was suggested by Folklow that it would seem there were two types of histamine receptors while the one type was blocked by classical antihistamines like mepyramine, diphenhydramine, chlorpheniramine, the other receptor type behaved obliviously to these classical antihistamines.

| Acetylcholine | Histamine | Parietal cell
|
|--------------|-----------|----------------|

These and other observations were to lead to the characterization of histamine receptors as H₁ - receptors (capable of being blocked by classical antihistamines) and H₂ - receptors lacking in any interaction with classical antihistamines.

The Search for H₂ - receptor Antagonists

Dr. Sir James W. Black championed the chemical approach to developing H₂ receptor antagonist at the Smith Kline and French (SKF) Research Laboratories in Welwyn Garden City in 1964.

The chemical approach to designing a suitable H₂ receptor antagonist was predicated on the fact that a well-defined biological concept of competitive antagonism was in place. The lead compound was histamine itself.

<table>
<thead>
<tr>
<th>Mepyramine</th>
<th>Diphenhydramine</th>
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Many structural derivatives were synthesized and tested biologically.
In the first 4 years about 200 compounds were made and tested. None of these gave the desired result.

Guanylhistamine

A curious observation by the physiologists then pointed to the fact that the substituents (R₁ and R₂) on the compounds tested biologically were lipophilic in character. On incorporating some hydrophilic compounds the physiologists observed some measure of H₂-receptor antagonism with one compound.

With increase in the methylenes group in the side chain (–CH₂) from 3 to 4 and subsequent methylation of the extant NH₂ group gave rise to the drug Burimamide.

Burimamide

Burimamide demonstrated the desired potent pure competitive antagonist activity. Burimamide was an extremely important compound and it provided a vital breakthough. It fulfilled all the criteria required for characterizing the existence of Histamine H₂ - receptor, other than H₁ receptors.

This discovery was announced in 1972 by Dr. James Black’s group after 6 years of intense research.

Burimamide antagonized the action of Histamine in stimulating gastric acid production in rat, cat and dog. When given intravenously in man, Burimamide blocked the action of histamine as an inducer of gastric acid in man.

Burimamide had one drawback. On administering it orally to man, its potency waned, because of extreme ionization. The guanidino group conferred a high pKa on Burimamide which ionized out at physiological pH 7.4 hence a decrease in absorption.

\[
\log K^+ = 3.4 \left( \delta_{\text{H}}^{\text{methyl}} - \delta_{\text{H}}^{\text{a}} \right) \quad \text{... 1}
\]

\[
\text{Frac. (a)} = \frac{[a]}{[a] + [b]} = 1 + K^+ \quad \text{... 2}
\]

\[
\text{Frac. (a + b)^+} = \frac{1}{1 + \text{antilog.} (7.4 - pK_b)} \quad \text{... 3}
\]

\[
pA_2 (\text{corr.}) = \text{pA}_2 - \log \left( \frac{\text{Frac.(a)}}{\text{Frac.(a + b)^+}} \right) \quad \text{... 4}
\]

Fig. 4: Tautomerism between Imidazole Species and Relationship to Physiological pH.
To increase the population of unchanged tautomeric form of
burimamide at the receptor site and hence its potency, it
was reasoned that an electron withdrawing atom e.g. S or
position 2 of the burimamide side chain would reduce the
proportion of imidazole ring in burimamide, which will encourage
higher population of tautomers and inherent H₂ antagonist
to

cytostatic in the stomach attest to the fact that both histamine
and gastrin are somehow linked in the gastric acid process.
Cimetidine was marketed first in the United Kingdom
in November 1976, in the USA in August 1977 and in
Japan in 1982. By 1999 Cimetidine had become known
as Tagamet in over all the world. Cimetidine changed the
medical management of peptic ulcer disease in the most
successful manner.
The research project was initiated in 1964 and the
arduous exercise came to fruition in 1976 - in spite of
considerable difficulties and disappointments. A typical
case study in Drug Design and Drug Discovery.
In 1983 Cimetidine's (Tagamet) annual worldwide
sales reached the level of nearly $100,000,000.
Subsequently, some other clinically effective anti-ulcer
drugs were introduced and these include

- Thiaburimamide
- Metiamide

An optimum antagonist potency was observed with
metiamide which was introduced into medicine for use in
the treatment of gastric and duodenal ulcers.

Although metiamide was pharmacologically and
clinically effective - clinical trials were to reveal its kidney
damaging propensity, agranulocytosis and low incidence
of reversible granulocytopenia.

It was suspected that these demerits had to do with
the thio urea group in the molecule. A consideration of
available isosteric groups to thiourea i.e. based on

essentially similar physicochemical properties strongly
identified the cyanoguanidine group for a possible isosteric
exchange with the thiourea group.
This structural modification (biostersmerism) gave rise
to a clinically effective and highly successful H₂ - receptor
antagonist Cimetidine which is free from the side effect of
granulocytopenia which limited the clinical use of
metiamide.
A relatively recent school of thought has implicated a gut residing bacterium Helicobacter pylori in ulcers. Literature is replete with the role of H. pylori in ulcerogenic lesions. The position of the chemist is that wounds and sores are traumatic and mechanical abrasions and in some cases chemical abrasion might the necessary cause of such wounds as in ulcer. Infection is a secondary factor.

But then advances in gastroenterology would rather suggest that the successful management of ulcer wounds should incorporate therapeutic and chemotherapeutic interventions.

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