High Dose Ketoconazole
Plus Hydrocortisone (HDK+ HC)

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Overview
Ketoconazole is a synthetic antifungal agent used to treat fungal infections since the 1970s. When given at traditional doses of 200-400mg/day to treat fungal infections, it was noted to temporarily decrease testosterone and adrenal androgen levels. Higher doses (800-1200mg/day) produced a longer hormone blockade with bound and free testosterone equally decreased. The concentration of ketoconazole appeared to be the reason for the more complete blockade.1

High-dose ketoconazole (HDK) is an oral broad-spectrum anti-prostate cancer (PC) agent that has testosterone lowering effects through its abilities to decrease both testicular and adrenal production of androgens by blocking various endocrine pathways. Thus, it is a form of androgen deprivation therapy. More specifically, HDK is classified as a P450 enzyme inhibitor and has also been shown to have direct cell killing action on PC cells.2 As a result, HDK plus hydrocortisone (HC), which is needed to replace natural cortisol production that may be lost when Nizoral is used, may be a reasonable treatment approach for men with prostate cancer (PC) for whom primary androgen deprivation therapy (ADT) was insufficient.

Ketoconazole is the generic name for Nizoral®

The treatment of systemic prostate cancer is often a progressive selection of therapies based on the cancer cell population. ADT is usually the first treatment selected when the PC is diagnosed as systemic. The object of ADT is to reduce the androgens that are promoting PC growth. Primary ADT usually consists of an LHRH agonist such as Lupron (leuprolide acetate) or Zoladex (goserelin acetate) plus an anti-androgen such as Casodex (bicalutamide) or Eulexin (flutamide). And some physicians use a third combination of drugs: finasteride (Proscar) and dutasteride (Avodart). If PC tumors are primarily comprised of “androgen-dependent” cells, ADT may control tumor activity for an extended period of time. Proper management of ADT requires measuring the testosterone to assure that a castrate level is maintained. This concept was covered in detail in the August 2001 and October 2001 issues of Insights.

PC that no longer responds to ADT is sometimes mistakenly identified as “hormone refractory” (HRPC) while in reality it often responds to secondary hormonal manipulations such as HDK, aminoglutethimide (AG) or the synthetic estrogen, DES (diethylstilbestrol). This article is devoted to the overview and discussion of HDK+HC.

Since PC is so unique in its inherent sensitivity to changes in levels of male sex hormones, trying HDK plus HC may be an option if it becomes clear that primary ADT is no longer fully effective in suppressing testosterone. HDK can rapidly lower serum testosterone to castrate levels by mechanisms that are different from LHRH agonists and anti-androgens. For example, HDK administration results in a decline in serum testosterone within 30 minutes and a 90% reduction by 48 hours3 (see Figure 1).
HDK also has a direct cytotoxic effect on the prostate cancer cell (see Figure 2). *In vitro* tests of two human cell lines of androgen-independent prostate cancer, PC-3 and Du-145, showed that HDK had direct cell-killing effects at serum values that were clinically attainable (1.1 to 10.0 mcg/ml).  

**Figure 2**

*Effect of ketoconazole on DU-145 & PC-3 androgen-independent cell lines*

Published clinical trials of HDK involved studies in the pre-PSA era and in the current era of using PSA as a surrogate biomarker of disease response. In the pre-PSA era, Pont, et al reported an 88% decrease or disappearance in pain in 17 previously untreated men with metastatic PC. Two of these patients remained in complete remission with no manifestation of disease after 30 months of treatment.
Muscato et al reported on 21 patients treated with HDK and HC that were considered to be hormone-refractory. Seven of 21 patients, or 33%, had a greater than 90% fall in PSA with six of these seven maintaining remissions lasting greater than 12 months (range 14-35+ months).

In a 1997 paper, Small et al reported the results of HDK + HC therapy in men with progressive disease after ADT and after anti-androgen withdrawal. Of 48 evaluable patients, 30 (62%) had a PSA decrease of greater than 50% for at least eight weeks while 23 of these (48%) had a decrease in PSA of greater than 80% also maintained for at least eight weeks. The PSA dropped to 0.3 ng/ml or less in five patients for 3+, 4+, 5+, 7+ and 10+ months. These same five patients had PSA values of 22, 47, 15, 488 and 6.7 ng/ml, respectively prior to initiating HDK + HC. For all 48 of these patients, the median PSA decrease was 79% (range 0-99%). The median duration of response was 3.5 months with 23 of the 48 patients having ongoing responses (range 3.2+ months to 12.3+ months). No difference was seen in response rates despite the presence or absence of an anti-androgen withdrawal response (AAWR). The median survival of all patients had not been reached at 6+ months.

In another 1997 abstract, Small et al described a treatment of 20 patients with simultaneous AAW and HDK + HC. Fourteen of these patients (70%) had a greater than 70% drop in their serum PSA level, and in 10 patients (50%) the decline in PSA level was greater than 80% compared to baseline levels. Six of the 10 were still responding after 2+ to 9+ months.

PCRI co-founders Scholz and Strum conducted a 60-patient study that concluded that “prolonged response with ketoconazole is far more common in HRPC patients if treatment is initiated before the baseline PSA (bPSA) rises above 10.” The results showed that patients with a bPSA of less than or equal to 10 had a median duration of response (MDR) of 25 months. Patients with a bPSA of greater than 10 had an MDR of only four months.

Decrease in bone pain has frequently been reported with HDK therapy. In 1984, Trachenberg published his findings of 13 patients who completed at least 6 months of treatment with HDK 400mg every 8 hours. HDK greatly reduced the need for analgesics, serum prostatic acid phosphatase levels dropped to normal and testosterone levels were reduced. The side effects in this group were reported as limited.

In 1988, 22 patients were followed at MD Anderson Hospital in Houston who had stage D2 disease in spite of previous androgen deprivation therapy. 16 patients reported pain as a significant part of their clinical picture prior to HDK. Of these patients, 13 (81%) noted improvement in bone pain for 1-8 months (mean three months). Subjective improvement in bone pain was also reported by others using HDK in hormone refractory PC patients. Since bone pain can affect quality of life, a trial of HDK with HC may be appropriate if bone pain is a part of the clinical picture for those whose PC has progressed while on ADT.

**High-Dose** (e.g. 400 mg, three times a day) ketoconazole is not the only approach. In 2002, Harris et al published a study with LDK (Low-Dose Ketoconazole) that included 28 patients with progressive prostate cancer despite castrate levels of testosterone and ongoing testicular androgen suppression. Treatment consisted of low dose ketoconazole (200 mg. three times daily) and replacement doses of oral hydrocortisone (20 mg. every morning and 10 mg. at bedtime). Thirteen (46%) of the 28 patients had a PSA decrease of more than 50%. The authors concluded: “The regimen of low dose ketoconazole with replacement doses of hydrocortisone is well tolerated and has moderate activity in patients with progressive androgen independent prostate cancer”. This treatment
may be a reasonable option for those who cannot tolerate larger doses of ketoconazole, i.e. HDK, but who may benefit from a secondary hormonal manipulation. LDK is certainly of interest for further investigation.

**Administration guidelines for HDK + HC**

HDK is initially prescribed at a dose of 200 mg three times a day for one week, then the dose is increased to 400 mg (two tablets) three times a day thereafter. HC is normally prescribed at a dose of 20 mg with breakfast and 10 or 20 mg with dinner. **HC should be taken with food.** If symptoms suggest HC excess (ankle swelling or diabetes in poor control), the dose may need to be decreased. **NOTE:** Do not abruptly discontinue HC. Always discontinue HC by tapering the dose with the guidance of your physician. This may take several weeks.

Unlike HC, **HDK should be taken on an empty stomach** (30-60 minutes before or at least two hours after food) because HDK requires acidity for dissolution. Stomach acid is needed to enhance HDK absorption (bioavailability). Patients take HDK on an empty stomach so that food there will not act as a buffer and interfere with the absorption of HDK. Moreover, histamine 2 (H-2) receptor antagonists (e.g. Zantac, Tagamet, Pepcid, Axid) decrease HDK absorption by 75%. Proton-pump inhibitors (Prilosec, Prevacid, Nexium) reduce acid even more. Antacids and Carafate will also interfere with HDK bioavailability. Many other drugs have the potential to interfere with the absorption of HDK by their anticholinergic side effects that decrease stomach acid. These include, but are not limited to the following (check with your physician):

| Artane (trihexyphenidyl) | Levsin (hyoscyamine) |
| Atrovent (ipratropium) | Levsinex (has hyoscyamine) |
| Beelith (has magnesium) | Librax (has clidinium) |
| Bellergal (has belladonna) | Lomotil (has atropine) |
| Bentyl (dicyclomine) | Pro-Banthine (propantheline) |
| Cogentin (benztropine) | Robinul (glycopyrrolate) |
| Cystospaz (hyoscyamine) | Transderm-V (scopolamine) |
| Ditropan (oxybutynin) | Urised (has hyoscyamine) |
| Donnatal (has belladonna) | Urispas (has hyoscyamine) |

If a patient has a medical condition under a doctor’s care to lower his stomach acid, taking HDK with Coca Cola or Pepsi (Diet OK), lemonade, orange juice, or 1000 mg Vitamin C is a reasonable option to increase absorption of HDK. Medical Oncologist and clinical researcher, Dr. Snuffy Myers does not recommend grapefruit juice be used in this setting. Grapefruit juice does not effectively acidify the stomach and its impact on ketoconazole has not been documented and may lead to accumulation of HDK resulting in toxic drug levels. A recent study done in patients who were taking acid-reducing drugs showed a 50% increase in ketoconazole bioavailability when it was taken along with a carbonated beverage.13
It should also be kept in mind that as people age, they may produce less stomach acid. This could have an impact on HDK absorption. Therefore, adding 500 mg of asorbic acid may be wise to avoid this concern. Check with your physician.

**Monitoring Nizoral Blood Levels**

HDK bioavailability (serum Nizoral or ketoconazole levels) can be monitored by a commercially available blood test. Our ability to assess this biological marker makes HDK therapy unique. Since there are many variables associated with absorption of HDK, a laboratory test of this nature is invaluable. Pont et al\(^\text{14}\) and Heyns et al\(^\text{15}\) reported on the value of serum HDK monitoring and their correlation with lowering androgen levels and clinical response.

Some oncologists have long recommended a Nizoral blood level of at least 4.0, which should be tested at four hours past the morning dose.\(^\text{16}\) They also recommend that patients wait at least three weeks after initiating HDK+HC therapy to ensure that the drug has obtained full strength in the blood stream. This theory is reinforced by the works of Eichenberger\(^\text{17}\) and Witjes in 1989.\(^\text{18}\)

It is therefore suggested that after a patient has been on HDK for three weeks or more, a Nizoral blood level be obtained at four hours after the morning dose of HDK. The PCRI Helpline staff may be able to assist callers in locating a laboratory that offers this testing.

**Side Effects**

The most common side effects are weakness or lack of strength, gastrointestinal complaints such as nausea or vomiting, liver toxicity, skin reactions, and a potential risk of adrenal suppression.

It is important to emphasize that any nausea or loss of appetite a patient may experience after initiating HDK + HC usually improves over time. It is inadvisable for patients on HDK to self-medicate with acid-blocking medications, antacids, or other over-the-counter (non-prescription) items without consulting a physician. Because stomach acid is necessary for absorption of HDK, use of antacids will limit HDK’s effectiveness.

Table 1 lists reported side effects from HDK+HC therapy found in peer-reviewed literature. They are displayed in order from most common to least common.

<table>
<thead>
<tr>
<th>Table 1. Side Effects From HDK+HC Treatment</th>
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<tr>
<td>Patients in Study</td>
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<tr>
<td>Skin toxicity (Sticky skin only)</td>
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<tr>
<td>Skin toxicity (Sticky skin, easy bruising, dryness)</td>
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<tr>
<td>Elevated liver enzymes</td>
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<td>Nausea/vomiting</td>
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Of all the side effects, liver damage may be the greatest concern. As HDK is being reevaluated for treatment of PC, it has become clearer that liver function test (LFT) abnormalities are mild to moderate and in most cases return to normal without intervention. **In some patients, however, liver function tests can become elevated to unhealthy and even dangerous levels.** Any risk factor for elevated LFTs such as a history of hepatitis or a regimen of other liver-affecting medications should be taken into consideration when using HDK. Patients on HDK must have liver function tests checked monthly.

Table 1 indicates that skin toxicity is a significant side effect in two of the studies, although a search of the literature does not indicate it to be as common as one would expect based on this data. Acquired cutaneous adherence, or Sticky Skin Syndrome, seldom causes sufficient discomfort for therapy to be withdrawn. However, Sticky Skin Syndrome can cause painful physical discomfort in patients using HDK and has been described as sitting on a vinyl chair on a hot day while wearing shorts. It can also result in an uncomfortable adhesion of thighs or under arms.

Small et al report that the principal side effects of HDK are related to gastric irritation leading to nausea and anorexia in at least 10% of patients. These side effects are due to mild adrenal insufficiency caused by such high doses of HDK. Cortisol, a specific type of steroid called a glucocorticoid, regulates glucose and one’s ability to deal with stress and is essential for life. Mild loss of cortisol production results in fatigue and nausea. Cortisol is produced in a **diurnal** pattern with peaks in the early morning hours gradually dropping through the day to lower levels. When stress increases such as with illness, injury, or surgery, and cortisol are blocked by HDK, one can go into shock and die. Life threatening cortisol deficiency is uncommon for men using HDK for PC, but mild adrenal cortisol deficiency is common. The use of hydrocortisone appears to diminish these side effects and may even enhance HDK’s ability to reduce testosterone for steroids have long been known to have androgen deprivation properties and are often employed in the treatment of PC.

It has been suggested by some that those taking HDK with HC carry an ID card or Medic Alert bracelet indicating the possible need for supplementary doses of HC during periods of stress. Ask your pharmacist or doctor how to obtain this card.

Intolerance of HDK side effects such as nausea, fatigue or abnormal liver function tests are the most common reasons patients stop this treatment. Fortunately, AG combined with hydrocortisone is rarely associated with nausea or liver function abnormalities, and it can be effectively substituted for HDK in some patients.

**Drug Interactions and Precautions:**

*Note: the following is not an all-inclusive list of all drugs that may interact with HDK. Make sure that
the administering physician has a complete list of your current medications and supplements. Also, check a current version of the Physician’s Desk Reference (PDR) for personal validation.

**HDK should not be taken with**

**Antihistamines:** Seldane (terfenadine), Claritin (loratadine) and Hismanal (astemizole). (Although Hismanal has been withdrawn from the U.S. market, patients may still have access to it.) HDK significantly increases the blood levels of these drugs, which can potentially cause serious cardiovascular side effects.

**Oral anti-diabetic medications:** Diabinese (chlorpropamide), Glucotrol (glipizide), DiaBeta, Glynase or Micronase (glyburide), Glucophage (metformin) and Tolinase (tolbutamide): HDK may increase the blood sugar-lowering effects of these drugs and result in severe hypoglycemia.

**Other types of medications:** Propulsid (cisapride): Propulsid is a medication that promotes gastrointestinal tract motor activity. When given with HDK, Propulsid may cause lethal cardiac rhythms. Although Propulsid is no longer generally available in the U.S., patients may still have access to it.

**Drugs that may need dose changes if HDK is taken concurrently:**

**Anticoagulants** (blood thinners): e.g. Coumadin (warfarin): HDK increases the blood-thinning effect of Coumadin which may require a dosage reduction.

**Anti-epilepsy agents:** Dilantin (phenytoin): Dilantin may affect the body’s ability to eliminate HDK and vice-versa, leading to blood level changes for both drugs that can lead to toxic symptoms.

**Anti-infective agents:** Rifamate contains isoniazid and rifampin: HDK causes adverse changes (up or down) in the blood levels of isoniazid; Rimactane (Rifampin): significantly reduces the blood levels of kenoconazole.

**Sleeping pills and tranquilizers:** Halcion (triazolam) and Versed (midazolam): HDK significantly increases the blood levels of both drugs.

**Other types of medication:** Medrol (methylprednisolone): HDK increases the blood levels of Medrol; Sandimmune (cyclosporine): Sandimmune may affect the body’s ability to eliminate HDK and vice-versa, leading to changes in the blood levels of both drugs. Statins (fluvastatin, pravastatin, simvastatin) may increase with use of HDK.

**WARNING:**

**HDK should not be taken with alcohol!**

Concurrent HDK and alcohol-containing beverages may cause an “Antabuse reaction” (skin flushing, rash, swollen legs, nausea, vomiting and headache).

**Chemotherapy Agents**

HDK is synergistic with some chemotherapy agents, such as adriamycin. However, HDK blocks the enzymes that clear taxol, taxotere, Emcyt, vincristine and vinblastine, just for starters. Specifically,
HDK blocks the cytochrome P450-containing protein, CYP 3A4, which is the enzyme responsible for clearing 50% of all prescription drugs. Recent investigation indicates this activity may enhance various chemotherapy agents. For example, a chemotherapy drug is usually cleared in the liver by cytochrome P450 so the patient does not get the full strength of the dose he is taking. When HDK is used, P450 is inhibited so he gets the full strength of this medication. Clinical trials must be undertaken to prove this, but it does appear that HDK may play a role in chemotherapy treatment in the future.

Each and every drug given to a patient on HDK needs to be very carefully evaluated. One must proceed with extreme caution when using ketoconazole with chemotherapy agents such as the taxanes. A dramatic dosage reduction of the chemotherapy (up to 80%) may be needed.

**Vitamin D Inhibitor**

Ketoconazole is an inhibitor of Vitamin D, and P450 enzymes are needed for metabolism of Vitamin D compounds. Calcitriol is the active form of Vitamin D. Therefore, men on HDK may be at risk for a Vitamin D deficiency and bone mass loss. Monitoring serum calcitriol could alert one to the need for calcitriol replacement. Combining Ketoconazole with calcitriol may enhance the anti-tumor actitivities of Vitamin D compounds and address the side effects of Vitamin D deficiency most likely associated with HDK treatment while posing very few if any additional side effects.

**Cost of HDK**

Generic HDK tablets currently cost approximately $2.00 per 200 mg tablet. At six tablets a day, this is a comparatively reasonable cost for an anti-tumor therapy. Hydrocortisone 20 mg tablets are currently available as generic brands for approximately 20 cents each. Patients having access to pharmacies in Mexico or Canada can purchase Nizoral 200 mg tablets for less.

**Conclusions**

HDK + HC is a very active regimen in the management of PC. With its broad spectrum of pharmacological activity, HDK is one of the most active agents used in the treatment of PC. Moreover, it can block the enzymatic degradation of multiple anti-cancer agents. What’s more, blood level monitoring can be used to evaluate absorption and hence the bioavailability of this anti-cancer agent.

Because of these unique properties, HDK has great potential for the therapy of prostate cancer. However, the FDA has never approved the use of HDK for the treatment of PC, and many physicians are unaware of the efficacy of HDK or are afraid of its toxicity based on exaggerations of HDK’s effect on the liver. Certainly, physicians should consider the use of HDK for active therapy of PC and well-designed trials should be undertaken and/or completed to provide a better understanding of the pharmacology of antineoplastic agents.

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